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HODGKIN'S DISEASE*

II. Pathology

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IN THE present paper there will be discussed the gross and microscopic features of the three types of Hodgkin's disease, the apparent site of origin in each and the extent to which each form involves the various organs of the body. Without some knowledge of the gross pathology and the distribution of the lesions one cannot hope to have a clear understanding of the clinical capacities of the disease.

HODGKIN'S PARAGRANULOMA

Hodgkin's paragranuloma appears to be a disease essentially of the lymph nodes. Those involved are most frequently found in the neck and are usually few in number, discrete, of rubbery consistence and not attached to the surrounding tissue (Table 1).

TABLE 1. *Apparent Primary Site of Disease in Cases of Hodgkin's Paragranuloma.*

	No. of Cases
Cervical lymph nodes	23
Inguinal lymph nodes	2
Axillary lymph nodes	1
Total	26

They are rarely more than 3 cm. in diameter and on cut section are yellowish gray. There is no evidence of softening or necrosis, and the capsule is intact.

On microscopic examination the normal structure of the lymph node as a whole is occasionally unaffected; more commonly it is partly or entirely lost. In some cases the lymph follicles are preserved and show only varying degrees and types of cellular activity; in others they are partly or completely obliterated. The peripheral sinus may be clearly outlined or be compressed by the follicles or obscured by actual cellular infiltration.

The diagnosis is based on the presence, within the involved nodes, of Reed–Sternberg cells, which may be few or numerous. They occur especially in the pulp; more rarely they are seen in the lymph follicles. These large cells with multilobed or more rarely multiple nuclei and prominent nucleoli are indistinguishable from those found in the other forms of Hodgkin's disease. The cytoplasm is fairly abundant and tends to be amphophilic. Mitotic figures in the Reed–Sternberg cells of this form of Hodgkin's disease are not numerous.

The predominant cell of Hodgkin's paragranuloma is, however, the adult lymphocyte. In cases in which the lymph follicles have been obliterated, the diffuse infiltration of the nodes by lymphocytes may be so great that an erroneous diagnosis of lymphocytoma is easily made. Buried within this mass of lymphocytes are found, nevertheless, the typical Reed–Sternberg cell, for which a careful search must be made not infrequently. Reticulum cells, often containing phagocyted débris, are present in varying numbers. In some cases they occur as focal aggregates resembling the lesions of Boeck's sarcoid. Plasma cells are not uncommonly seen and may be numerous. Eosinophils are sometimes present, but never in such quantities as in Hodgkin's granuloma.

The pathologic process never invades the capsule, although there may be an infiltration of this structure by scattered lymphocytes and plasma cells. In Hodgkin's paragranuloma one never sees the necrosis, the infiltration with polymorphonuclear leukocytes, the marked eosinophilia or the fibrosis so frequently found in Hodgkin's granuloma.

The changes in the reticulum vary widely. In some cases it is normal in amount; in others there is an increase in the number of fibers in the medullary cords but not in the follicles. In still others the fibers are thickened, but this change is usually associated with scarring due to some independent and unrelated process.

It should be pointed out that in certain cases of Hodgkin's paragranuloma the presence of fairly numerous eosinophils and fibrin is evidence that

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a transformation into the granulomatous form is impending, and transitional types of the disease occur in which it is difficult to be sure whether one is dealing with Hodgkin's paragranuloma or with Hodgkin's granuloma. It may be argued that those cases of Hodgkin's paragranuloma that fail to change into Hodgkin's granuloma represent, indeed, an entirely different disease. It must be remembered, however, that those that progress cannot, in their incipiency, be distinguished from those that do not. For instance, in 1910 one of our patients had a cervical lymph node removed that showed the typical picture of Hodgkin's paragranuloma. Subsequent biopsies from the neck in 1917 and 1936 showed a histologic picture indistinguishable from that seen in 1910. The patient has continued to be in good health to date. On the other hand, a second patient in 1941 had a cervical lymph node removed that showed the typical histologic picture of Hodgkin's paragranuloma. He was given a moderate amount of high-voltage x-ray treatment and continued in apparently good health until 1943, at which time he suddenly became progressively worse, with all the signs and symptoms usually associated with advanced Hodgkin's granuloma. Autopsy showed extremely extensive involvement with the granulomatous type of the disease. The initial biopsy specimens from these two cases were indistinguishable. In the first case, the type of lesion did not alter over a period of twenty-six years, and the patient was alive and active thirty-eight years after the initial lymphadenopathy had been noted. In the second case, on the other hand, the histologic picture changed with considerable rapidity and death shortly ensued. A third patient had a large mass of nodes dissected from the neck in 1920. He remained active and in apparent good health until 1943, when he returned with a large mediastinal mass and a few lymph nodes in the neck. These proved on biopsy to be Hodgkin's granuloma. In 3 other cases, Hodgkin's granuloma developed as proved by autopsy. Four patients died of unrelated causes such as carcinoma or tuberculosis, and 5 died from causes unknown. Unfortunately, no autopsy was obtained in any of the latter cases. Thirteen patients are alive and active, although some still show evidence of their disease.

It should be emphasized that so long as the pathologic process remains unaltered the prognosis is relatively good, but in certain cases Hodgkin's granuloma develops, and the prognosis then becomes that of the latter condition.

If the pathologic process remains that of Hodgkin's paragranuloma, involvement of the internal organs appears to be rare. In 4 cases, the mediastinal nodes became involved. Three of these patients are still alive, and 1 died of pulmonary tuberculosis. In 2 cases, the spleen became definitely enlarged. Each of these patients died at home of unknown causes. In 3 cases, both the mediastinal nodes and spleen became involved. All these patients have died. There were no autopsies.

Hodgkin's Granuloma

The granulomatous process may involve isolated groups of nodes in certain regions, or the process may be widespread. In our series of cases, the lymph nodes were implicated to some extent in every case. Cases have been reported, however, in which the disease was confined to a single organ with no lymph-node involvement, such as the 2 cases mentioned by Sternberg[1] in which the spleen alone was diseased.

From autopsy studies of 59 cases, it is shown that the retroperitoneal and para-aortic lymph nodes were the most frequent primary site of the disease, followed by other lymph nodes and the stomach or intestines (Table 2). This is in sharp contrast to the clinical observations, from which it appears that the cervical nodes were the primary site in an overwhelming percentage of the cases. It is probable that the favorable response of the more superficial nodes to x-ray therapy and the difficulty of recognizing during life involvement of the deeper nodes and internal organs account for this apparent discrepancy. But the fact that internal lymph nodes are so frequently involved at autopsy and primarily so, even though they have been suspected of being implicated during life, should make the physician cautious before deciding, in a given case, that the disease is confined to a small number of obviously involved but comparatively localized superficial nodes.

Table 2. *Primary Site of Disease in Cases of Hodgkin's Granuloma.*

Site	No. of Cases	
Lymph nodes		53
Retroperitoneal	17	
Para-aortic	13	
Mediastinal	9	
Cervical	8	
Mesenteric	6	
Gastrointestinal tract		6
Stomach	3	
Duodenum	1	
Small intestine	1	
Large intestine	1	
Total		59

The diseased lymph nodes often occur in masses, but the outlines of each can usually be made out. Their consistence may be soft or firm, but with deposition of connective tissue the nodes become increasingly harder. Only rarely, however, do they assume the stony hardness so suggestive of carcinoma. The cut surface is grayish white, often with a brownish tint. It may be homogeneous or may show foci of necrosis, which are of varied shape and are white to yellow. In our experience, breaking down or softening due to Hodgkin's granuloma alone does not occur. Secondary in-

fection, particularly in the groin, may, however, give rise to abscess formation or the deposition of scar tissue to such an extent that a definitive diagnosis is impossible. If feasible, it is always wise to avoid the removal of a node from the groin and to choose for biopsy a lymph node in the neck or axilla, provided that there is one of sufficient size and that it is readily accessible.

The histologic picture of Hodgkin's granuloma is characterized by the presence of Reed–Sternberg cells and by its great pleomorphism. The lymph nodes involved as a rule show complete loss of their normal architecture. The germinal centers and the cords of lymphatic tissue as well as the sinuses are obliterated. Extension of the process into the capsule may occur. It must be remembered that in any given case the histologic picture in the nodes in different regions or even in different nodes in the same region may vary widely.

The typical Reed–Sternberg cell measures from 12 to 40 microns in diameter. Its shape is often irregular, and cytoplasmic processes frequently extend between neighboring cells. The nucleus, in its most characteristic form, is lobulated or multilobed. Multinucleated forms also are seen. Small forms of the Reed–Sternberg cell may occur, and in these the nucleus is round or oval. The chromatin occurs in heavy clumps, and large nucleoli are a prominent feature. The cytoplasm, which is abundant in proportion to the nucleus, varies in its staining reaction from acidophilic to basophilic, tending to be basophilic in the younger forms. In sections of tissue fixed in Zenker's fluid and stained with Mallory's phloxin-methylene blue stain, the cytoplasm often appears finely reticulated.

In sections stained for reticulum, the Reed–Sternberg cells often contain numerous silver-positive granules. In such sections these cells are often found closely applied to the reticulum fibers, and in some cases these fibers seem to pass through the cytoplasm. When stained with Penfield's modification of Hortega's silver carbonate method for microglia, the Reed–Sternberg cells tend to become impregnated, as do phagocytes of mesenchymal origin, as shown by Dunning and Furth[2] and as noted by us in unpublished studies. As a general rule, there is an increase in the number of reticulum fibers, which either run between single cells or enclose groups of cells. As sclerosis advances, the fibers tend to be thicker and more numerous. In a completely fibrosed node, the major portion of the intercellular substance is dense collagen.

Mitotic figures are not uncommon, and multiple mitoses are occasionally seen. Phagocytosis by Reed–Sternberg cells is uncommon. There is a strong tendency, however, for them to undergo necrobiosis. Thus, in a section of Hodgkin's granuloma scattered degenerating and pyknotic Reed–Sternberg cells are frequently found, and this feature is often an aid in diagnosis when one may be in doubt whether true Reed–Sternberg cells are present.

In supravital preparations, the cytoplasm has a ground-glass appearance, and in some cells a delicate, finely granular rosette stained with neutral red can be seen in close proximity to the nucleus.

The exact origin of the Reed–Sternberg cells has not been proved, but we agree with those workers who believe that they are derived from the sinus endothelium and from reticulum cells. In favor of such an origin is their resemblance to these cells, especially when the Reed–Sternberg cells are small and mononuclear. A more striking resemblance is seen in the cells of Hodgkin's sarcoma and of anaplastic reticulum-cell sarcoma, in which the differential diagnosis must rest on the presence or absence of Reed–Sternberg cells. It is, of course, extremely important to differentiate normal reticulum cells and Reed–Sternberg cells. When the latter are large and typical, no difficulty should be encountered. When, however, they are small and the nuclei are not multilobed, the differential diagnosis depends on the character of the nucleus. The nucleus of a reticulum cell has finely divided, scattered chromatin and lacks a prominent nucleolus, whereas a Reed–Sternberg cell has its chromatin arranged in large masses and is characterized by one or more prominent nucleoli.

Cells occasionally confused with Reed–Sternberg cells are multinucleated plasma cells, foreign-body giant cells, Langhans giant cells, tumor giant cells and megakaryocytes. The last two may present great difficulties in differential diagnosis. Tumor giant cells, however, rarely occur singly as do Reed–Sternberg cells, and they are accompanied by other tumor cells characteristic of the neoplasm at hand. Foreign-body giant cells and Langhans cells have nuclei varying in number from several to twenty or more, and the nuclei in each of these types of cells are regular in shape, equal in size and orderly in arrangement. The chromatin is finely divided, and nucleoli are not prominent. Megakaryocytes closely resemble Reed–Sternberg cells, and given a single cell it is almost impossible to determine which of the two it is, although megakaryocytes do not have prominent nucleoli and their nuclei, although multilobed, are always single. The diagnosis must therefore depend on the picture of the section as a whole. To illustrate the difficulty of a definitive diagnosis, we refer to a nodule in the skin removed from a patient with proved myelogenous leukemia. Megakaryocytes were a prominent feature, and a number of highly competent pathologists without hesitation diagnosed the disease as Hodgkin's granuloma.

The nature and significance of the Reed–Sternberg cell is entirely obscure. It has been considered a tumor giant cell by those who consider Hodgkin's granuloma a neoplasm. In our opinion, it is probably a peculiar reactive form of the reticulum cell

in response to the agent causing the disease. In support of this conception is the cellular reaction to infection with *Bacillus mallei*, in which, as is well known, a characteristic type of giant cell is seen. It is our opinion that in like manner the Reed–Sternberg cell of Hodgkin's granuloma is the response to the unknown etiologic agent of that disease.

The number of Reed-Sternberg cells in granulomatous nodes varies widely. In some they are few in number; in others they are numerous, and may occur in groups as well as scattered. Rarely if ever are they so scarce as in paragranuloma.

In addition to the Reed–Sternberg cells, there are many other types of cells, and a pleomorphic picture is indeed characteristic of the disease. Lymphocytes are usually numerous. Plasma cells are almost constantly present, their number varying from a few to so many that a diagnosis of plasmocytoma may be entertained. One of the most outstanding features of the histologic picture of Hodgkin's granuloma, as first pointed out by Goldmann,[3] is the presence of eosinophils. They are practically always present, although their number varies widely. In addition, polymorphonuclear neutrophilic leukocytes can usually be found, and are particularly prominent when the inflammatory reaction is extremely active and necrosis is present. Activity on the part of the reticulum cells, as evidenced by hyperplasia and hypertrophy, is frequent, sometimes with the formation of focal lesions resembling tubercles or Boeck's sarcoid.

In addition to the pleomorphic cellular content, two other changes are found that are characteristic of the granuloma — necrosis and fibrosis. The necrosis varies in extent from minute microscopic foci to large areas easily visible grossly. It is often of the infarct type, the cell outlines being preserved in the necrotic area. Polymorphonuclear leukocytes and reticulum cells may be found at the periphery of necrotic areas. Fibrin formation is common. Occasionally giant cells of the foreign-body type are present. The necrotic areas are eventually organized by the ingrowth of the fibroblasts of the stroma. As the processes of necrosis and fibrosis proceed, some lesions finally come to be largely composed of connective tissue, often dense and sometimes hyaline, in the interstices of which can be seen a few Reed–Sternberg cells. A high degree of fibrosis does not necessarily mean a long-standing process; on the contrary, it may represent a favorable reaction on the part of the host. Several patients when first biopsied have shown such a picture in their nodes, and their subsequent course has been relatively favorable.

As is well recognized, radiation therapy produces a high degree of sclerosis. In such nodes, however, even though markedly fibrosed, an occasional Reed–Sternberg cell can always be found.

The lesions described above may vary considerably in the different organs or tissues of any given patient. For example, some lesions present a marked inflammation with but little necrosis, others show extensive necrosis, and in still others fibrosis is the outstanding feature. The type of histologic picture depends presumably on such factors as the activity of the process, the age of the lesion and the reaction of the host to the causative agent.

Occasionally, as Sternberg[1] has pointed out, large amounts of lipoid are found in the reticulum cells and in giant cells of the foreign-body type. The significance of this phenomenon is not clear, but that it may occur must be recognized in order to avoid the error of making a diagnosis of one of the diseases of disturbed lipoid metabolism, such as Niemann–Pick's disease or Gaucher's disease, and of overlooking the essential granulomatous lesion.

Some authors have described another feature as not uncommon, namely, amyloid formation. In our experience this has been extremely rare.

The granulomatous form of Hodgkin's disease is frequently associated with active tuberculosis. It has been said that tuberculosis follows Hodgkin's disease like a shadow. The two processes may exist side by side in the same organ, and although grossly one may be confused with the other, the histologic characteristics of each are so definite that no difficulty in distinguishing them should be encountered.

The lymph nodes were involved at autopsy in every case in this series, and it is noteworthy that the involvement was usually widespread and of fairly uniform distribution (Table 3).

Aside from the generalized lymphadenopathy, almost every organ of the body with the exception of the central nervous system proper may be invaded (Table 4). This fact accounts for the extraordinarily protean clinical manifestations.

TABLE 3. *Lymph Nodes Found to Be Involved at Autopsy in 59 Cases of Hodgkin's Granuloma.*

TYPE OF NODE	NO. OF CASES
Mediastinal	55
Para-aortic	34
Cervical	30
Retroperitoneal	28
Mesenteric	28
Inguinal	25
Axillary	25

The spleen is involved in a large percentage of cases. In Sternberg's[1] series it showed lesions in 80 per cent, in Terplan's[4] in 65 per cent, and in Uddströmer's[5] in 63 per cent. In our series it was involved in 75 per cent. The involved organ may be normal in size or enlarged to a marked degree. The largest spleen in this series weighed 1245 gm. and the smallest 120 gm., with an average of 480 gm. The lesions appear as circumscribed focal areas, gray to yellowish and varying in diameter from that of a miliary tubercle to a centimeter or more. As a rule, the

lesions in each spleen are of approximately the same size. Foci of necrosis similar to those seen in lymph nodes may occur. The picture produced by the focal lesions contrasting with the red color of the uninvolved portion has led to the terms "porphyry"[6]

TABLE 4. *Organs Found to Be Involved at Autopsy in 59 Cases of Hodgkin's Granuloma.*

ORGAN	No. OF CASES	
Lymph nodes		59
Spleen		44
Liver		31
Bones*		27
Vertebra	25	
Sternum	3	
Rib	3	
Ilium	2	
Femur	1	
Skull	1	
Lung		24
Pleura		10
Infiltration only	5	
Effusion only	3	
Infiltration and effusion	2	
Gastrointestinal tract		10
Stomach	4	
Small intestine	4	
Duodenum	1	
Cecum	1	
Peritoneum		10
Ascites only	9	
Ascites and infiltration	1	
Kidneys		8
Pancreas		8
Pericardium		8
Effusion only	6	
Infiltration only	2	
Adrenal glands		7
Diaphragm		3
Uterus		2
Breast		2
Skin		2
Thyroid gland, trachea, aorta, ovary, bladder		1 each

*Multiple involvement.

and "*Bauerwurst*"[7] spleen. The spleen has been described as the sole site of the disease.[1] In our series other organs were always involved.

Histologically, the lesions in the spleen resemble those in the lymph nodes.

The liver is frequently affected. It was involved in 38 per cent of Sternberg's cases and in 53 per cent of our series. Massive enlargement of the liver is in our experience rare. The largest liver weighed 3500 gm. In 29 of the 59 autopsied cases the organ weighed more than 1800 gm., and in 18 of these foci of Hodgkin's disease were noted. On the other hand, of the 16 livers weighing less than 1600 gm. only 4 were involved. The focal, circumscribed nodules are similar to those in the spleen, or there may be grayish streaks of diseased tissue following the distribution of the portal areas. If fibrosis is extensive, scars may be produced in such a manner that healed gummas are simulated. Some authors have described the lesions as resembling those of cirrhosis. Bile stasis due to compression of the bile ducts by the surrounding granulomatous tissue, resulting in jaundice, does occur, but it is rare. The small lesions tend to occur in the portal areas. Their histologic composition and pattern are similar to those of the lesions in lymph nodes. The large foci may cause compression and destruction of the surrounding liver tissue.

Statistics concerning the incidence of involvement of bones in Hodgkin's granuloma are unsatisfactory because of the incompleteness of examination of the osseous system.[8] In a recent review of Hodgkin's granuloma with special reference to the involvement of the bone marrow, Steiner[9] collected from the literature 547 autopsied cases, of which 153 (28 per cent) showed lesions of the bone marrow. In his own 14 cases, he found the marrow involved in 11 (78 per cent); it should be pointed out that he examined sixty-two bones in the 14 cases. In our series involvement of the bones occurred in 61 per cent of those cases in which the osseous system was examined. Such a figure is, however, obviously inaccurate because of the limitations in making a thorough gross and microscopic study of the bones in each case. The bones most commonly involved at autopsy in order of their frequency are the vertebras, especially the lower thoracic and upper lumbar, and much more rarely the sternum, ribs, pelvis, femur and skull. Multiple involvement is not uncommon. The lesion may be confined to the marrow, or the process may invade and destroy the cortex, leading in the case of the vertebras to collapse, which if extensive may result in compression of the cord, although it is surprising to what extent collapse can occur without clinical symptoms. Involvement of the bones may be metastatic or by extension from neighboring organs. Grossly the lesions appear as grayish to yellowish nodules that stand out against the remnants of the normal marrow. Although fibrosis of the involved marrow often occurs, osteosclerosis is rare.

Histologically, the lesions may be miliary in type, composed of typical granulomatous tissue with but little disturbance of the bony architecture, or extensive, causing destruction of the bony trabeculae. The process replaces the normal marrow, and at the periphery of the process great activity on the part of the hematopoietic tissue may be present. In a specimen of marrow removed by biopsy, unless a certain degree of fibrosis is present, great difficulties may be encountered in making a definite diagnosis because of the similarity of the megakaryocytes to Reed-Sternberg cells.

Versé[10] estimated from a study of his own material and from the cases reported in the literature that approximately one third of the cases show involvement of the lungs. Sternberg[1] stated that of his 52 autopsied cases, 15 (29 per cent) showed such lesions. Pulmonary involvement was found in 41 per cent of our cases. The lesions may be divided into three types. In the first type, there appears a large, tumorlike mass, often involving the greater part of a lobe. Such a condition may easily be mistaken, both by x-ray and grossly at autopsy, for bronchiogenic carcinoma. In the second type, grayish streaks of diseased tissue follow the course of

the bronchi and usually represent an extension from affected mediastinal and tracheobronchial lymph nodes. Invasion of the walls of the bronchi with compression or even occlusion of their lumens may occur. In the third and rarest type, there are small to medium-sized circumscribed nodules scattered diffusely through the parenchyma.

Histologically, the process shows wide variations. The granulomatous tissue may fill the alveoli without destroying their walls; on the other hand, the normal structures may be entirely destroyed and replaced by the granuloma. In some cases very little connective tissue is present, the alveoli, however, containing numerous Reed–Sternberg cells. Such a cellular type of lesion may be confused with Hodgkin's sarcoma, but in the lymph nodes and other organs from the same case the usual typical granulomatous process is present and post-mortem diagnosis is not difficult. In other cases fibrosis is such an outstanding feature that the lesion resembles an organized pneumonia and careful search is necessary to detect Reed–Sternberg cells lying in the interstices of the dense connective tissue. All variations between the distinctly cellular type of process and the highly fibrotic are encountered. Cavity formation is rare and probably represents, when it does occur, a pyogenic infection of the granulomatous tissue, although in some cases, if a bronchus has been occluded, it is of the nature of a bronchiectatic abscess. The formation of lesions beneath the visceral pleura is not uncommon. The pleura is reported by Sternberg[1] as being occasionally involved. In 5 of our autopsied cases there was infiltration of the pleura without effusion, in 3 there was serous effusion only, and in 2 there was serous effusion together with infiltration of the pleura. In no case was the effusion bloody. In every case in which there was effusion the mediastinal nodes were involved.

Hodgkin's granuloma in the gastrointestinal tract may be either primary or secondary. The secondary type is usually the result of the invasion from adjacent diseased lymph nodes or other organs. In addition, secondary lesions appear as nodules in the serosa or mucosa as the result of metastasis from a generalized granulomatous process.

In our series of autopsies there were 6 cases of Hodgkin's granuloma primary in the gastrointestinal tract. Three were primary in the stomach, 1 in the ileum, 1 in the duodenum and 1 in the cecum. These figures are in essential agreement with those of Sternberg.

Grossly the gastric lesion may appear as a polypoid, tumorlike mass projecting into the lumen or as a broad-based ulcer with firm raised edges. It may lead to thickening of practically the entire wall, with marked accentuation of the normal rugae. This probably gives rise to the so-called *Gehirnaspekt* in x-ray films of the stomach, considered by some as diagnostic of the disease. There is usually extension to neighboring lymph nodes. In rare cases only the local gastric lymph nodes are involved and no other organs or tissues show evidence of the granulomatous process.

Microscopically, the lesions in the stomach vary considerably. In some cases the process is composed of numerous Reed–Sternberg cells, many eosinophils and some lymphocytes and plasma cells, with little or no fibrosis. In other cases the granulomatous infiltration shows a moderate or a marked degree of fibrosis in addition to the characteristic cytologic elements. If there has been ulceration, the picture is further complicated by superficial necrosis and the presence of numerous polymorphonuclear leukocytes.

According to the literature,[11, 12] the intestinal granulomatous process is most frequently situated in the duodenum or the jejunum. In our series there were lesions in the lower small intestine in 4 cases, in the duodenum in 1 and the cecum in 2. The lesions appear as flat ulcers with raised, rather firm edges and with irregular, granular bases. The bowel wall may be entirely encircled. The granulomatous process also appears as plaques or tumorlike nodules that may obstruct the lumen and lead to intussusception. Cases have been reported in which erosion of an artery at the base of a granulomatous ulcer has resulted in a fatal hemorrhage. In 1 of our cases, not included in the autopsy series because there was only an incomplete post-mortem examination, rupture of the small intestine resulted in the sudden death of a patient who had appeared the day before to be in excellent condition. The possibility of such sudden deaths must always be borne in mind. Microscopically, the lesions resemble those found in the stomach.

In 9 of our autopsied cases there was marked ascites, in only 1 were there actual lesions in the peritoneum. In all cases having ascites there was involvement of the retroperitoneal nodes.

Involvement of the kidneys when the granulomatous process is widespread is not unusual. In our series it occurred in 14 per cent of the cases. There are usually small circumscribed nodules, situated especially in the cortex. We agree with Sternberg that massive lesions are distinctively rare. The histologic picture needs no comment. The ureters may be affected by extension of the process from neighboring lymph nodes.

Secondary involvement of the pancreas by extension of granulomatous lesions of the stomach, small intestine or retroperitoneal nodes is not very uncommon; it occurred in 8 of our cases. Primary involvement was not found, although it has been described in the literature.[13]

The heart muscle was not invaded in any case, but in 2 cases there were small nodules on the parietal pericardium. Terplan and Mittelbach[4] report such lesions as being frequent. In 6 other cases in our

series there was a moderate (100 to 300 cc.) serous effusion.

Twelve per cent of our cases showed involvement of the adrenal glands. In each case there had been extension of the granulomatous process from adjacent lymph nodes. Sternberg's experience was similar.

The uterus was involved microscopically in 2 of our cases.

Implication of the ovaries is rare. In 1 of our cases there was a microscopic lesion.

Sternberg[1] reports 2 cases of Hodgkin's granuloma of the thyroid gland. In 1 of our cases there were metastatic lesions in this organ.

In none of our cases was the prostate gland involved; Sternberg mentions 1 case reported in the literature. No involvement of the testis or epididymis was found, although a rare case has been described in the literature.[4]

Sternberg found granuloma of the tonsil in 5 of his 52 cases. The tonsils were enlarged and ulcerated. In none of our cases were the tonsils involved.

Rarely there is invasion of the diaphragm, breast, skin and certain other organs (Table 4).

Lesions of the central nervous system proper do not occur. Compression of the cord due to extradural masses or periosteal infiltrations of the vertebras, however, is not infrequent. In our series no case showed such lesions at autopsy. Clinical evidence of meningeal involvement is, however, not uncommon. It should be mentioned that patients with Hodgkin's granuloma may show signs and symptoms indicating cerebral involvement, yet at autopsy no demonstrable anatomic change can be found. During life 1 of our patients had extraordinary disturbances of taste and complete anorexia, yet extremely prolonged and careful examination of the nervous system failed to reveal even a microscopic lesion.

Hodgkin's Sarcoma

Studies of 27 autopsied cases show that Hodgkin's sarcoma usually has its origin in the retroperitoneal lymph nodes and that the lesion is characteristically invasive and destructive.

The disease was primary in the retroperitoneal nodes in 19 (70 per cent) of our cases (Table 5), and

Table 5. *Apparent Primary Site of Disease in Cases of Hodgkin's Sarcoma.*

	No. of Cases
Retroperitoneal lymph nodes	19
Stomach	3
Tonsil	2
Mediastinal lymph nodes	1
Para-aortic lymph nodes	1
Lung	1
Total	27

in all the involvement was extensive and extremely destructive. In 1 case, there was a retroperitoneal mass of confluent lymph nodes weighing in the aggregate 1600 gm. and direct extension from these nodes to the second and third parts of the duodenum, the stomach, the head of the pancreas and the lower surface of the liver. In addition, there was compression of the common bile duct, and the aorta was buried in and partially compressed by a mass of firm, elastic nodes extending from the diaphragm to the bifurcation of the iliac vessels. In another case, a mass of lymph nodes extended along the entire length of the abdominal aorta, and the tumor infiltrated the right psoas and the right latissimus dorsi muscles, filled the entire right abdominal gutter and extended from deep within the pelvis to the twelfth right rib, which was compressed and eroded by the tumor. In a third patient, the lymphadenopathy extended from the level of the pancreas into the true pelvis.

Of the remaining 8 cases, the disease was primary in the stomach in 3, in the tonsil in 2, and in the lung, mediastinum and para-aortic nodes in 1 each. The lymph nodes were involved to a varying degree in every case, and peripheral lymphadenopathy was not uncommon (Table 6).

As might be expected, the retroperitoneal tumors resulted in many complications, such as hydronephrosis, obstruction of the common bile duct and venous thrombosis due to compression by or invasion from adjacent tumor. The tendency to invade neighboring structures such as the pancreas, adrenal glands and muscle was marked.

Table 6. *Lymph Nodes Found to Be Involved at Autopsy in 27 Cases of Hodgkin's Sarcoma.*

Type of Node	No. of Cases
Retroperitoneal	21
Mediastinal	14
Mesenteric	12
Axillary	11
Cervical	10
Inguinal	9
Para-aortic	4

The involved nodes were enlarged, often greatly so. In some cases their outlines could be recognized; in others the tumor had invaded the capsule, resulting in a large, irregular-shaped conglomerate mass. In consistence, the tumor may be fairly firm or soft or even practically diffluent. As a rule, however, the tissue cuts with ease, and the cut surface is grayish white to white. Areas of necrosis are not infrequent, and appear as yellowish foci that may be extremely small or very extensive.

Histologically, the tumor is composed of cells two or three times the size of a normal lymphocyte. The nucleus is usually round but may be ovoid. The majority of the cells have single spherical nuclei with prominent nucleoli, but Reed-Sternberg cells with multilobed nuclei are always seen. Their presence is necessary to establish the diagnosis of Hodgkin's sarcoma. These cells vary in number considerably from case to case, being numerous in some and few

and far between in others. It is our belief that the cells with a single spherical nucleus are undifferentiated forms of the Reed-Sternberg cell. This theory is sustained by the staining reactions, the character of the chromatin and the presence of transitional forms. The cytoplasm of the tumor cells tends to stain neutrophilic or basophilic. When stained with Mallory's phloxine-methylene blue, after Zenker fixation, the cytoplasm often has a granular or reticulated appearance. Mitotic figures are usually numerous, as would be expected in a highly malignant tumor.

Apart from the tumor cells, there are usually only scattered lymphocytes and reticulum cells. The former are readily identifiable by their comparatively small size and the characteristically dense masses of chromatin. Reticulum cells are easily recognizable by their finely divided, scattered chromatin and acidophilic cytoplasm. Neutrophils, eosinophils and plasma cells are rarely found unless the tumor is located in a region exposed to complicating inflammatory infiltration. Areas of necrosis, usually of the infarct type, are not infrequent. It should be emphasized that the diagnosis of Hodgkin's sarcoma rests, in the last analysis, on the presence of Reed-Sternberg cells.

With silver stains, the reticulum fibers are usually found to be increased in number. They enclose groups of cells as well as single cells. In some cases the fibers are not only more numerous but also somewhat thickened.

The structure of the affected node is destroyed by the diffuse growth of the tumor cells. The capsule may be intact or may be extensively invaded, with extension of the neoplasm into the surrounding tissues.

Aside from the lymph nodes, the organs most frequently involved in our series were the liver, the gastrointestinal tract, the pancreas, the bones and the lungs (Table 7). The liver was involved to a greater or less degree in 16 cases (59 per cent). In 10 of these, the tumor occurred as grayish-white nodules scattered throughout the parenchyma. The size of such nodules varied widely from case to case, but in each case they were of approximately the same size. The smallest foci averaged 2 mm. in diameter and the largest measured several centimeters. In some cases only two or three tumor nodules could be found, whereas in others the organ was studded with them. In 3 cases, the tumor was situated only in the capsule. In 3 cases, there was direct extension into the liver, either from the stomach or from the retroperitoneal nodes.

On the whole, the liver was somewhat enlarged, the largest weighing 2900 gm., but the majority weighed approximately 2000 gm., and it is notable that in a number of cases the liver, although definitely involved, was no larger than normal, the few metastatic nodules being buried deep within its substance.

Various portions of the gastrointestinal tract were involved in 15 cases (55 per cent). This is in sharp contrast to the comparatively uncommon involvement of the gastrointestinal tract in Hodgkin's granuloma. In 3 cases, the disease was primary in the stomach. In one of these, the tumor involved

TABLE 7. *Organs Found to Be Involved at Autopsy in 27 Cases of Hodgkin's Sarcoma.*

ORGAN		NO. OF CASES
Lymph nodes		27
Liver		16
Gastrointestinal tract*		15
Stomach	8	
Small intestine	4	
Duodenum	4	
Colon	4	
Esophagus	1	
Pancreas		11
Bones*		10
Vertebras	7	
Skull	3	
Pelvis	2	
Ribs	1	
Femur	1	
Lungs		10
Adrenal glands		9
Spleen		9
Kidneys		8
Muscles		5
Central nervous system		4
Pituitary gland	3	
Cerebellum	1	
Pericardium		4
Gall bladder		3
Thyroid gland		2
Tonsil		2
Testicle		2
Ovary, uterus, iliac vein, bladder and dura		1 each

*Multiple involvement.

the posterior wall in its middle third, extending from the greater to the lesser curvature and causing an ulceration over an area measuring 12 by 4 cm. There was considerable erosion at the base of the ulcer, and extensive hemorrhage had taken place from it. The tumor was white and necrotic and cut easily. In another case, the tumor appeared as a craterlike ulcer, 4 cm. in diameter, situated 2 cm. above the pylorus. The edges of this area were elevated 0.3 to 0.4 cm. above the surrounding mucosa and were made up of moderately firm, white tissue. The center of the crater was soft and homogeneous. On section, the tumor was found to extend into the pancreas and between the vertebral bodies. In the third case, the tumor occurred at the cardiac end of the stomach and involved an area 14 cm. in diameter. From the mucosal aspect, the neoplasm appeared as a plateaulike elevation, one portion of which was cauliflowerlike, and measured 4 cm. in diameter; the surface was ulcerated and greenish gray. The tumor tissue was homogeneous, pinkish gray and soft.

In 5 other cases, the stomach was secondarily involved. In one, the tumor appeared as an ulcer; in another, as raised patches in the mucosa. In a third, the stomach wall was invaded by primary tumor of the retroperitoneal nodes. In the other two cases, the tumor produced no visible macroscopic change.

There were no tumors primary in the small or large intestine. The small intestine or duodenum,

however, was secondarily involved in 8 cases, chiefly by metastasis. The lesions appeared as grayish-white nodules of varying size and number and were situated in the mucosa. In 2 cases the large intestine showed metastatic nodules in the mucosa, and it was invaded by extension of a primary tumor of the retroperitoneal lymph nodes in 2. In 1 case, there was a microscopic lesion of the esophagus.

It should be particularly noted that involvement of the gastrointestinal tract was not infrequently multiple and often extensive.

The pancreas was affected by tumor in 11 cases (41 per cent). In 1, the tumor was apparently metastatic from a primary lesion of the tonsil. The other cases represented direct extension from primary tumors of neighboring structures — the stomach in 3 cases and the retroperitoneal lymph nodes in 7.

The bones were examined in 22 cases. Ten of these showed tumor. In 7 cases, the vertebras were involved, the tumor appearing as grayish nodules surrounded by red, uninvolved marrow. In 3 cases, the skull had been invaded, twice by direct extension from tumors primary in the tonsil. In the first of these, there was a pedunculated growth on the superior part of the occipital bone. The region of the sella was markedly widened, and the pituitary was involved by soft, grayish tissue. The bony structures surrounding the fossa were softened. The tumor also occupied the entire sphenoidal sinus, had eroded the surrounding sphenoidal structures and was found as well in the foramen lacrum of the petrous portion of the temporal bone. In the second case, the tumor invaded and partly destroyed the antrum and bones of the orbit on one side. In the third case, involvement of the skull was apparently metastatic from the retroperitoneal lymph nodes. In the region of the right temple there was a superficial swelling of the scalp 8 cm. in diameter. The inner table of the skull beneath this was shaggy, and the entire thickness of the bone was involved by tumor that had extended through to the dura, which was diffusely invaded. There was, however, no extension to the pia-arachnoid.

There was 1 case of involvement of the great trochanter of the femur. In 2 cases, the tumor, primary in the retroperitoneal nodes, had extended directly to the pelvic bones. In another case, the ribs showed multiple tumors secondary to a primary lesion of the para-aortic lymph nodes.

Ten cases showed involvement of the lungs at autopsy. In 1, the tumor was primary in the right lower lobe, and owing to the extensive involvement and the apparently abrupt onset, the case on admission was mistaken for one of lobar pneumonia. At autopsy, the grayish-white tumor occupied practically the whole of the lower lobe and was necrotic in its center. In 2 cases, there were scattered nodules approximately 1 cm. in diameter. Two cases grossly showed no visible tumor but it was present microscopically. In the other 5 cases, the tumor had extended in from the mediastinal nodes along the bronchi.

The adrenal glands were involved in 9 cases, in each by direct extension from tumors arising in adjacent lymph nodes.

The spleen was involved in 9 cases, much less often — and far less extensively — than in Hodgkin's granuloma. In 1 case, there was direct extension from a tumor primary in the retroperitoneal lymph nodes, in the form of a yellow-white mass extending in from the hilus in a radial manner for some 6 cm. The splenic artery and vein were surrounded by the neoplasm but were not invaded by it. In 2 cases, the spleen showed only microscopic lesions. In the remaining cases there were one or more grayish-white nodules, varying in diameter from 0.1 to 1.0 cm. The involved spleens were uniformly but not greatly enlarged, the heaviest of them weighing 640 gm.

The kidneys were involved in 8 cases, in each of which the tumors were metastatic. In no case did they result from invasion from surrounding structures. In every case each kidney was involved to a similar degree. The tumor nodules were less than 1 cm. in diameter and were usually situated in the cortical region.

There was invasion by tumor of the muscles of the thoracic wall in 1 case, of the psoas muscle in 2, of the quadriceps in 1, and of the diaphragm in 1.

The central nervous system was involved in 15 per cent of the autopsies. Again one sees the sharp contrast between Hodgkin's sarcoma and Hodgkin's granuloma, in which, so far as we are aware, no involvement of the central nervous system proper has been reported. In 1 case, the tumor was primary in the paravertebral lymph nodes and had extended between the transverse process of the vertebras from the third cervical to the eleventh dorsal, invading the dura and causing marked compression of the spinal cord in the upper cervical region. In another, there was a metastasis from a primary tumor of the retroperitoneal lymph nodes to the cerebellum. This was described as a ridge of tumor measuring 5 by 3 by 0.5 cm. and extending along the superior surface of the cerebellum. Microscopic examination revealed extensive invasion of the cerebellum well into the dentate nucleus.

The pituitary gland was involved in 3 cases. In 1 case, in which the tumor was primary in the tonsil, the gland was invaded and its normal structure obliterated. In another, it was surrounded and compressed by neoplastic tissue but was not actually invaded. In the third, microscopic examination revealed invasion of the capsule and the peripheral portion of the pars nervosa; the tumor was primary in the retroperitoneal lymph nodes.

In 3 cases, there was a moderate serous effusion into the pericardial sac, and in another a small nodule of tumor was seen in the parietal pericardium itself.

In 3 cases, there were small metastatic nodules in the gall bladder.

In 2 cases, the thyroid gland was implicated, each time by a metastasis secondary to tumor primary in the retroperitoneal nodes. In 2 cases, metastatic nodules were found in the testes.

There was involvement by the tumor of the following organs in 1 case each: ovary, uterus, iliac vein, bladder and dura.

Summary

Hodgkin's paragranuloma, characterized by the presence of Reed–Sternberg cells in the absence of necrosis or fibrosis, appears to be a disease essentially of lymph nodes. With the passage of time, it may become transformed into the more malignant Hodgkin's granuloma.

Hodgkin's granuloma, characterized by the presence of Reed–Sternberg cells, pleomorphism, eosinophils, necrosis and fibrosis, may involve any organ of the body with the exception of the central nervous system proper and is frequently widespread.

Hodgkin's sarcoma, characterized by the presence of typical Reed–Sternberg cells scattered among cells that are probably extremely anaplastic forms of Reed–Sternberg cells, behaves as a true tumor, is highly invasive and malignant and may involve any organ of the body, including the central nervous system proper.

Transitional forms of these three types of Hodgkin's disease occur, but it is essential for the understanding of the clinical features to recognize the existence of each.

References

1. Sternberg, C. Lymphogranulomatose und Reticuloendotheliose. *Ergebn. d. allg. Path. u. path. Anat.* **30**:1-76, 1936.
2. Dunning, H. S., and Furth, J. Studies on relation between microglia, histiocytes and monocytes. *Am. J. Path.* **11**:895-914, 1935.
3. Goldmann, E. E. Beitrag zu der Lehre von dem "malignen Lymphom." *Centralbl. f. allg. Path. u. path. Anat.* **3**:665-680, 1892.
4. Terplan, K., and Mittelbach, M. Beiträge zur Lymphogranulomatose und zu anderen eigenartigen, verallgemeinerten Granulomen der Lymphknoten. *Virchows Arch. f. path. Anat.* **271**:759-866, 1929.
5. Uddströmer, M. *On the Occurrence of Lymphogranulomatosis (Sternberg) in Sweden 1915–1931 and some Considerations as to its Relation to Tuberculosis.* 225 pp. Copenhagen: Lund, 1934.
6. Benda, C. Zur Histologie der pseudoleukämischen Geschwülste. *Verhandl. d. deutsch. path. Gesellsch.* **7**:123-131, 1904.
7. Janz, Zur Operation der leukämischen Milz. *Beitr. z. klin. Chir.* **23**: 287-293, 1899.
8. Uehlinger, E. Über Knochen-Lymphogranulomatose. *Virchows Arch. f. path. Anat.* **288**:36-118, 1933.
9. Steiner, P. E. Hodgkin's disease: incidence, distribution, nature and possible significance of lymphogranulomatous lesions in bone marrow: a review with original data. *Arch. Path.* **36**:627-637, 1943.
10. Versé, M. Die Lymphogranulomatose der Lunge und des Brustfells. In *Handbuch der speziellen pathologischen Anatomie und Histologie.* Edited by F. Henke and O. Lubarsch. Vol. III. Part 3. 701 pp. Berlin: Julius Springer, 1931. Pp. 280-343.
11. Coronini, C. Ueber das Paltauf–Sternberg'sche Lymphogranulom mit besonderer Berücksichtigung der Veränderungen des Verdauungsschlauches und solcher an der Leberpforte mit und ohne Gelbsucht. Zugleich ein Beitrag über lymphogranulomatöse Gefässveränderungen. *Beitr. z. path. Anat. u. z. allg. Path.* **80**: 405-478, 1928.
12. Siegmund, H. Lymphogranulomatose. In *Handbuch der speziellen pathologischen Anatomie und Histologie.* Edited by F. Henke and O. Lubarsch. Vol. IV. Part 3. 1076 pp. Berlin: Julius Springer, 1929. Pp. 400-403.
13. Gruber, G. B. Lymphogranulomatose der Bauchspeicheldrüse. In *Handbuch der speziellen pathologischen Anatomie und Histologie.* Edited by F. Henke and O. Lubarsch. Vol. V. Part 2. 950 pp. Berlin: Julius Springer, 1929. Pp. 431-435.

PEMPHIGUS*

A Further Report on Chemical Studies of the Blood Serum and Treatment with Adrenocortical Extract, Dihydrotachysterol or Vitamin D

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As shown in two recent communications,[1, 2] significant changes in the electrolyte content of the blood serum occur in patients with pemphigus vulgaris. In an attempt to correct the chemical changes, we have treated patients with pemphigus vulgaris with adrenocortical extract, dihydrotachysterol or massive doses of vitamin D. In the first communication the results of treatment with adrenocortical extract in 5 patients with acute pemphigus were reported, and in the second the results of treatment with dihydrotachysterol in 10 patients with chronic pemphigus.

From 1939 to 1941, 17 additional patients with pemphigus were studied and treated at the Massachusetts General Hospital. It is the purpose of this paper to report the chemical findings in the blood serum of these patients and to evaluate the effectiveness of adrenocortical extract, dihydrotachysterol and massive doses of vitamin D in the treatment of this disease.

Diagnosis and Prognosis

The various types of pemphigus differ not only in their clinical appearance and prognosis but also in regard to chemical changes and their response to treatment. It seems best to describe briefly the clinical appearance and the prognosis of each type before presenting the chemical data and therapeutic results. The quoted figures regarding the prognosis of the various types were obtained from a series of 62 patients with pemphigus admitted to the Massachusetts General Hospital between

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TABLE I. *The Concentration of Various Constituents in the Blood Serum of Patients with Pemphigus.*

Type of Disease	Patient	Date	Total Base	Sodium	Potassium	Calcium	Chloride	Protein	Phosphate	Non-protein Nitrogen	Hematocrit	Clinical Status		Treatment
												General	Skin lesions	
		Normal Values	*m.eq./l.* 150–155	*m.eq./l.* 139–141	*m.eq./l.* 4–5	*m.eq./l.* 4.7–5.4	*m.eq./l.* 102–106	*gm./100cc.* 6.4–7.5	*mg./100cc.* 3.1–4.5	*mg./100cc.* 20–35	% 40–45			
Pemphigus vulgaris acutus	I.D.	10/16/40	152	139	4.4	4.8	100	7.5	3.6	33	48	Good	0 (only oral)	Dihydrotachysterol started 10/16/40; adrenocortical extract started 10/25/40.
		12/ 1/40	140	130		5.3		5.8		38		Poor	+++	
		12/ 7/40	156	142	3.8	8.4	104	6.4		80	27	Fair	+	
		1/31/41		134	3.9	7.1	95	6.0	4.6	71	22	Poor	+++	
		3/19/41		145		5.6		6.0		37	16	Died	++	
	R. M.	5/11/40	148	138	4.9	4.6	102	6.3		22	40	Fair	++	Vitamin D started 6/18/40.
		6/18/40		132		4.6	91	4.6		24		Poor	+++	
		6/27/40		139		6.6			4.0	27	21	Fair	+	
		9/ 1/40	146	133		6.8				28	32	Died	+++	
	H. D.	8/21/39	149	136	4.2	4.5	104	6.4	2.1	33		Fair	++	Dihydrotachysterol started 8/22/40; adrenocortical extract started 9/26/40.
		10/ 6/39		127		5.6		5.6	2.5	36	28	Poor	+++	
		1/ 2/40	146	135	4.1	4.9		6.4		43	30	Fair	+	
		7/31/40		139		5.9		7.2	2.4	37	40	Well	0	
Pemphigus vegetans	N. P.	10/11/40	154	143	5.1	4.5	103	6.3	4.2	32	39	Fair	+	
		10/19/40	141	129	5.1	4.3	91	5.5	4.1	31	38	Poor	+++	Dihydrotachysterol started 10/15/40; adrenocortical extract started 11/6/40.
		10/27/40	144	134	4.4	5.6	92	5.4		39	32	Fair	+	
		12/16/40		129	4.6	5.5	93	5.3				Poor	+++	
		1/14/41		149	4.5	6.0	116	5.0		53	38	Died	++	
	D. F.	4/20/40	142	131	4.8	4.0	99	4.5	3.4	46	39	Poor	+++	Adrenocortical extract started 4/20/40; vitamin D started 11/26/40.
		6/ 7/40	147	136	4.1	4.2	99	5.5	3.2	19		Fair	+	
		1/ 4/41		144		5.7		7.5		68		Good	(+)	
Pemphigus vulgaris chronicus	E. S.	3/12/40	151	141	4.4	4.3	106	5.3	2.0	26	41	Fair	++	
		5/25/40	143	133	4.9	3.9	98	5.6	1.2	29	37	Poor	+++	Dihydrotachysterol started 5/25/40; changed to vitamin D 6/21/40.
		7/19/40		135		6.7		7.2		37		Fair	+	
		11/19/40		145	4.8	5.3		7.9		59	43	Well	0	
	J. L.	6/ 5/40	148	137	4.2	4.1	106	6.2	2.7	19		Poor	+++	Vitamin D started 6/5/40.
		7/ 2/40	153	141	3.2	7.3	108	7.2		26		Fair	+	
		7/30/40		141		7.3		8.0		28		Good	(+)	
	D. P.	9/26/40	149	138	5.0	3.6	106	5.3	3.7	40		Poor	+++	Dihydrotachysterol started 9/30/40; changed to vitamin D 11/1/40.
		1/ 7/41	154	145		6.3		5.9		58	18	Died	+	
	A. J.	6/20/40	147	136	4.5	4.6	101	6.0	2.1	38	44	Fair	+++	Dihydrotachysterol started 7/19/40; adrenocortical extract given from 8/25 to 10/17; vitamin D instead of dihydrotachysterol after 11/13/40.
		8/ 8/40		131		4.8	100	6.4		24	35	Poor	+++	
		9/19/40		136		9.2		6.6		45	40	Fair	+	
		1/ 7/41	152	140		5.9		7.4		49	37	Well	0	
	I.W.	9/23/39		138		3.8		6.3				Fair	++	Vitamin D started 9/29/39.
		10/17/39	152	141	3.8	7.9	96	6.4	2.9	47	30	Good	+	

1921 and 1936, none of whom received any of the treatments under discussion. A detailed clinical study of this group of patients has been published previously.[3]

There are three well-established types of pemphigus, namely, pemphigus vulgaris, pemphigus foliaceus and pemphigus vegetans. To these, two new types have been added in recent years — pemphigus conjunctivae or benign mucous-membrane pemphigus[4, 5] and pemphigus erythematosus or Senear–Usher type of pemphigus.[6] Furthermore, Brocq[7] has suggested a division of pemphigus vulgaris into two types — an acute, malignant type (*pemphigus subaigu malin*) and a chronic, benign type. The septic (acute or butcher's) pemphigus, however, is no longer regarded as a disease entity. As stated elsewhere,[8] it is believed that cases that in the past have been reported with this diagnosis can be classified as bullous impetigo, severe erythema multiforme or pemphigus vulgaris acutus.

Clinical study of the patients with pemphigus at the Massachusetts General Hospital has shown that separate consideration of these three additional types is justified.

Acute Pemphigus Vulgaris Acutus

Descriptions of pemphigus vulgaris acutus (*pemphigus subaigu malin* or malignant pemphigus vulgaris) have been given by Brocq,[7] Lane and Lambert[9] and Pelagatti.[10] We[1, 11] have discussed the clinical picture in two recent communications. The bullas are usually small and flaccid and break easily. Occasionally no bullas form on the skin and the epithelium merely slides off, leaving erosions, which tend to enlarge as the epithelium becomes detached at the periphery. By peripheral extension and confluence of the erosions large areas of the body may become denuded. The large erosions, which are the most important clinical sign of this type of pemphigus, show little tendency to heal. The oral mucosa is involved in nearly all cases. The mouth is frequently the site of the first lesions. The oral involvement, if present, is usually severe. Large denuded areas may develop in the mouth, just as on the skin, by peripheral extension of the erosions. In the severest stage almost the entire oral mucosa may be transformed into a single large, eroded surface. Frequently the lesions extend to the vermilion border of the lips, and hemorrhagic crusts form on the lips.

A large percentage of the patients are Jewish. The mortality among 22 patients seen at the Massachusetts General Hospital between 1921 and 1936 was 100 per cent. The average duration of the disease was seven and a half months.

Pemphigus Vegetans

As stated in a previous communication,[11] pemphigus vegetans resembles pemphigus vulgaris acutus in every respect except the vegetations that form secondarily on the erosions. The prognosis is grave, although not quite so hopeless as that in acute pemphigus vulgaris. Frühwald,[12] in reviewing the outcome of 147 cases of pemphigus vegetans as reported in the literature, found the mortality to be 73 per cent. He believed, however, that some additional patients might have died subsequent to the time of publication.

Pemphigus Vulgaris Chronicus

In pemphigus vulgaris chronicus the bullas are usually tense and may attain considerable size, but do not break so easily as in the acute form of the disease. The erosions at the site of broken blisters do not extend at the periphery. The tendency of the erosions to heal is well pronounced. This form rarely starts in the mouth, and only about half the cases ever show involvement of the oral mucosa. The appearance of the oral lesions corresponds to that of the cutaneous lesions. One can frequently see intact blisters in the mouth, because they do not break easily. They are usually small, and the erosions at the site of broken blisters do not tend to increase in size, so that the oral involvement is never so extensive as in pemphigus vulgaris acutus.

Pemphigus vulgaris chronicus is apparently rare among Jews, since none of the patients with this form seen at the Massachusetts General Hospital since 1921 belonged to the Jewish race. The mortality in 16 patients seen between 1921 and 1936 was 50 per cent.

Pemphigus Foliaceus

Pemphigus foliaceus shows bullas only in the early stage and gradually assumes the appearance of a generalized exfoliative dermatitis, from which it is, however, easily differentiated by the presence of a positive Nikolsky sign. Oral lesions are absent. The mortality rate in the 14 patients with pemphigus foliaceus seen between 1921 and 1936 was 43 per cent. In those who survive, this disease may become extremely chronic. In 4 of the 14 patients who were first seen between 1921 and 1936, the disease has by now persisted for more than ten years. Age appears to be an important factor in the prognosis. In the patients who acquired pemphigus foliaceus before the age of thirty the mortality rate was 13 per cent; in those who acquired it at a later age it was 83 per cent.

Pemphigus Erythematosus

Many cases of pemphigus erythematosus (Senear–Usher type of pemphigus) may be regarded, as Gray[13] has suggested, as a localized form of pemphigus foliaceus that may remain localized or change into pemphigus foliaceus. This concept cannot, however, be applied to all cases, since several reports have appeared in which pemphigus vulgaris subsequently developed. Three cases of pemphigus foliaceus seen at the Massachusetts General Hos-

pital began as pemphigus erythematosus. The mortality is zero in the localized type, but in cases in which pemphigus erythematosus develops into pemphigus foliaceus or vulgaris the prognosis changes accordingly.

Pemphigus Conjunctivae

Pemphigus conjunctivae (benign mucous membrane pemphigus) always attacks the mucous membranes and, in about half the cases, the skin. The conjunctivas are nearly always affected and occasionally represent the only area of involvement. The lesions always produce scarring of the conjunctivas, frequently scarring of other mucous membranes and occasionally scarring of the skin. Pemphigus conjunctivae is an extremely chronic affection but is benign in its course. It never causes a general feeling of illness and does not end fatally.

Electrolyte Content of Blood Serum

The present series of 17 patients includes 3 with pemphigus vulgaris acutus, 2 with pemphigus vegetans, 6 with pemphigus vulgaris chronicus, 4 with pemphigus foliaceus and 2 with pemphigus conjunctivae. The chemical data confirm the findings previously reported.[1, 2] Significant changes in the electrolyte content of the blood serum were observed in pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vulgaris chronicus. No consistent changes were noted in pemphigus foliaceus and pemphigus conjunctivae.

In patients with pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vulgaris chronicus, the amount of sodium, chloride, calcium and protein in the blood serum was found to be reduced. Representative data of determinations at the time of admission and in the course of the disease are listed in Table 1. It is apparent that the degree of reduction usually corresponded to the severity of the clinical condition and to the amount of skin involved. In the earliest part of the disease, when only a few lesions were present, the chemical determinations usually showed normal values. For instance, patients I. D. and N. P., who at the time of admission showed only a few lesions, had normal values for nearly all constituents at that time. During the period of widespread cutaneous involvement the chemical changes were usually more pronounced in patients with pemphigus vulgaris acutus and pemphigus vegetans than in those with pemphigus vulgaris chronicus. The serum sodium was decreased in patients with pemphigus vulgaris acutus and pemphigus vegetans to values varying from 127 to 132 milliequiv. per liter, and in patients with pemphigus vulgaris chronicus to values varying from 131 to 138 milliequiv. per liter. The values for chloride closely paralleled those of the sodium. The protein was decreased to values varying from 4.6 to 5.8 gm. per 100 cc. in patients with pemphigus vulgaris acutus and pemphigus vegetans and to 5.3 to 6.2 gm. in patients with pemphigus vulgaris chronicus. The decrease of serum calcium is less evident because most patients, soon after admission received dihydrotachysterol or massive doses of vitamin D, both of which produce a rise of the serum calcium within a short time. Nevertheless it is evident, even from the values obtained at the time of admission, that a decrease of the serum calcium is usually present in patients with pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vulgaris chronicus.

In 4 patients with pemphigus foliaceus, chemical studies revealed no significant changes except that in 1 patient the serum protein was reduced to 4.3 gm. per 100 cc. None of the patients were, when studied, in the early bullous stage, but in the chronic exfoliative stage. It may be mentioned, however, that 1 patient of the previous series[2] who at the time of study had been in the early bullous stage had shown a reduction of the serum sodium to 136 milliequiv. per liter. Two patients with pemphigus conjunctivae showed normal values. Similarly, 1 patient with pemphigus erythematosus studied in the previous series[2] had shown a normal concentration of electrolytes in the blood serum.

Treatment with Adrenocortical Extract, Dihydrotachysterol and Vitamin D

Administration of adrenocortical extract produces an increase of sodium in the blood serum. This hormone has a sodium-retaining action, since it increases the reabsorption of sodium in the proximal segment of the renal tubules.[14] Dihydrotachysterol, as well as vitamin D, produces a rise of the calcium content of the blood serum and subsequently an increased elimination of calcium through the kidneys. The rise of the serum calcium is accomplished by increased absorption of calcium from the intestinal tract and by resorption from the bones.[15] A rise of the serum protein and serum sodium usually accompanies the rise of the calcium.[16]

The treatment with adrenocortical extract, dihydrotachysterol and vitamin D represents an attempt to correct the chemical changes observed in patients with pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vulgaris chronicus. It was found that adrenocortical extract was the most effective drug in pemphigus vulgaris acutus and pemphigus vegetans, whereas dihydrotachysterol or massive doses of vitamin D produced the best results in pemphigus vulgaris chronicus. In several patients combined treatment with adrenocortical extract and dihydrotachysterol was used.

Adrenocortical extract was found in general to be superior to the synthetic preparation. The recommended dosage is 20 cc. a day for the first four days, and 5 to 10 cc. a day thereafter. Half the daily dose is injected intravenously and half intramuscularly. In addition, either an intravenous infusion of 1000 cc. of physiologic saline solution or 10 gm. of salt

in enteric-coated capsules is given daily. If the synthetic drug is used, the daily dosage recommended is 3 cc. intramuscularly during the first week, and 1 or 2 cc. thereafter. One thousand cubic centimeters of normal saline or 10 gm. of salt is also given daily. No toxic effects were observed as a result of this plan of treatment.

Dihydrotachysterol and vitamin D, which have a similar action on the calcium metabolism of the body, were found to possess the same degree of effectiveness. The optimal therapeutic effect was observed when the concentration of the serum calcium was raised above the normal level of 5 milliequiv. to a concentration of 6.5 to 7.5 milliequiv. per liter. This effect was usually accomplished by giving 10 or 15 cc. of dihydrotachysterol for seven to fourteen days. The serum calcium was maintained at this level in most cases by giving 3 to 5 cc. of dihydrotachysterol a day. Seventy-five thousand units of vitamin D was found to correspond approximately to 1 cc. of dihydrotachysterol in their calcium-raising effect. The two dangers of this treatment — namely, hypercalcemic coma with subsequent circulatory collapse and renal damage through mechanical obstruction of the tubules by calcium deposits — have been discussed in detail in the previous paper.[2] It had been stated that dihydrotachysterol and massive doses of vitamin D must be given with great circumspection to persons older than sixty and that it is contraindicated in patients with demonstrable renal insufficiency. Careful control of the level of calcium and nonprotein nitrogen is required. These determinations should be carried out twice a week during the first few weeks and later once a week.

Administration of dihydrotachysterol or vitamin D in the recommended doses produced a rise of the calcium level above normal in all patients so treated (Table 1). The rise usually began within one week. The effect of adrenocortical extract was less uniform. The rise of the sodium occurred often only after several weeks of treatment and, before the rise occurred, a continued decrease of the sodium was occasionally noted when the condition of the skin became worse.

Results

Treatment with adrenocortical extract, dihydrotachysterol or massive doses of vitamin D produced some favorable results in pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vulgaris chronicus, the three types of pemphigus in which a reduction of the serum sodium, chloride, calcium and protein occurs. The results of treatment in pemphigus foliaceus, pemphigus erythematosus and pemphigus conjunctivae, in which no significant chemical changes are observed, were in general disappointing.

Fifteen case reports of patients treated with adrenocortical extract or dihydrotachysterol were given in the two previous communications.[1, 2] For this reason, no case histories will be given here but the cases of each type will be discussed collectively.

Pemphigus vulgaris acutus. A total of 7 patients with pemphigus vulgaris acutus received treatment with adrenocortical extract, dihydrotachysterol or massive doses of vitamin D. Four of them died of pemphigus and 3 survived, a mortality of 57 per cent, compared with 100 per cent in 22 patients admitted between 1921 and 1936 who did not receive this treatment.

The course of 4 cases under treatment with adrenocortical extract was reported in detail in the previous communication.[1] Two patients died of pemphigus, one of them, however, only after he had a complete, although short, remission. Two patients were reported as cured. One of them is still living and well, and the other has since died from cerebral hemorrhages without having had any more lesions of pemphigus.

Between 1939 and 1941, 5 patients with pemphigus vulgaris acutus were treated. Two of them died after less than two weeks' treatment. These cases have been excluded from statistical consideration, because death occurred before treatment could have taken full effect. Of the remaining 3 patients, 2 died of pemphigus after a prolonged period of treatment and 1 is living. The 2 patients who died after prolonged treatment first seemed to respond to the treatment in that they had a complete remission lasting several weeks, but then relapsed in spite of continued treatment. The 1 living patient has been free from lesions for three years. The improvement that was observed in all 3 patients of the present series began three to six weeks following institution of treatment.

The question arises whether the observed remissions might not have been spontaneous. This is possible, but spontaneous complete remissions in pemphigus vulgaris acutus are rare and were, for instance, not observed in any of the 22 cases of pemphigus vulgaris acutus seen between 1921 and 1936. An incidence of 6 complete remissions in the 7 cases of both series seems significant.

Two of the 3 patients of the present series were treated with both adrenocortical extract and dihydrotachysterol or vitamin D and 1 with vitamin D alone. The surviving patient received both types of treatment. It seems that in acute pemphigus vulgaris it is advisable to use both types of treatment.

Pemphigus vegetans. Three patients with pemphigus vegetans were treated. Two of them died of pemphigus and 1 survived.

The course of 1 case treated with adrenocortical extract was reported in the previous communication.[1] The patient died after having had a complete remission lasting for five weeks.

The present series includes 2 patients with pemphigus vegetans. One died after having undergone

a complete remission lasting two weeks; the other is living. Improvement was observed in both patients approximately two to three weeks after treatment was begun. The surviving patient has had a few lesions in the anogenital region and in the oral cavity most of the time since her first discharge three years ago. On two occasions she had moderately severe relapses, which, however, subsided within a few weeks after resumption of treatment.

In spite of the fact that 2 of the 3 patients of both series finally succumbed, it appears significant that no lesions of pemphigus present; the other 4 patients are living. The patient who died of pemphigus showed a satisfactory response so far as the cutaneous lesions were concerned, but had become extremely weak and anemic, death occurring when hypostatic bronchopneumonia developed. At the time of exitus only a few scattered, small bullas were present. Of the 4 living patients 3 are free from lesions and 1 occasionally develops a few lesions but is otherwise well. Two of the 3 patients who are free from lesions had a mild relapse after

TABLE 2. *Results of Treatment with Adrenocortical Extract, Dihydrotachysterol or Vitamin D.*

TYPE OF DISEASE	NO. OF PATIENTS	CURED	GREAT IMPROVEMENT	LITTLE OR NO IMPROVEMENT	DIED OF PEMPHIGUS	LIVING	DIED OF DISEASE OTHER THAN PEMPHIGUS
Pemphigus vulgaris acutus	7	3			4 (57%)	2	1
Pemphigus vegetans	3		1		2 (67%)	1	
Pemphigus vulgaris chronicus	14	11	1		2 (14%)	7	5
Pemphigus foliaceus	5		1	2	2 (40%)	3	
Pemphigus erythematosus	1		1			1	
Pemphigus conjunctivae	2			2		2	

all 3 patients showed complete remissions under treatment.

The surviving patient of the present series received treatment with adrenocortical extract, and the other received dihydrotachysterol. It is believed that, just as in pemphigus vulgaris acutus, the combined treatment with adrenocortical extract and dihydrotachysterol or vitamin D is advisable.

Pemphigus vulgaris chronicus. Fourteen patients with pemphigus vulgaris chronicus were treated. Two of them died and 12 survived, a mortality of 14 per cent, compared with 50 per cent in the 16 patients not so treated.

Eight of the 10 patients reported previously[2] as having been treated with dihydrotachysterol had pemphigus vulgaris chronicus. One of them was reported to have died from pemphigus, 4 as having died from other diseases with no lesions of pemphigus present, and 3 as living. These 3 patients are still living and well and have had no further treatment.

Six patients with pemphigus vulgaris chronicus were treated between 1939 and 1941. One died of pemphigus and 1 from cardiovascular disease with treatment had been discontinued but recovered when treatment was resumed.

In 3 of the 6 patients improvement began within two weeks, in the other 3 patients after three to six weeks of treatment. Three of the 4 patients who showed complete healing were free from active lesions six weeks after treatment was begun, but 1 patient ceased forming lesions only after three months of treatment.

The treatment in 4 of the 6 cases of the present series consisted of dihydrotachysterol in the beginning and vitamin D later. In 1 of these patients adrenocortical extract was also given for seven weeks because of an extremely low serum sodium (131 milliequiv. per liter). Two patients received only vitamin D. Dihydrotachysterol and vitamin D seemed to possess the same degree of effectiveness when given in corresponding doses.

TABLE 3. *Comparison of the Mortality Rates of Patients Treated with Adrenocortical Extract, Dihydrotachysterol or Vitamin D with Those of Patients Not So Treated.*

TYPE OF DISEASE	PATIENTS SO TREATED			PATIENTS NOT SO TREATED		
	NO.	DIED OF PEMPHIGUS	MORTALITY %	NO.	DIED OF PEMPHIGUS	MORTALITY %
Pemphigus vulgaris acutus	7	4	57	22	22	100
Pemphigus vegetans	3	2	67	—	—	(73)
Pemphigus vulgaris chronicus	14	2	14	16	8	50
Pemphigus foliaceus	5	2	40	14	6	43
Pemphigus erythematosus	1	0	0	—	—	—
Pemphigus conjunctivae	2	0	0	10	0	0

Pemphigus foliaceus. The previous report concerning treatment of chronic pemphigus with dihydrotachysterol[2] included 1 case of pemphigus foliaceus. This patient had come under treatment in the early stage of the disease when bullas were still present. The recovery under treatment with dihydrotachysterol was slow but satisfactory. The

patient has had occasionally during the last four years a few erythematous lesions on the skin, but the Nikolsky sign has been negative and he has been able to do heavy labor.

Four more patients with pemphigus foliaceus were treated between 1939 and 1941. All came under treatment at a time when bullas were no longer present. They presented the appearance of a generalized exfoliative dermatitis. All of them were treated with either dihydrotachysterol or massive doses of vitamin D. None of them showed improvement. Two died and 2 are living.

Pemphigus erythematosus. One case of pemphigus erythematosus treated with dihydrotachysterol was included in the previous report.[2] The patient had shown slow improvement. At present the patient still has a few scattered lesions.

Pemphigus conjunctivae. Two patients with pemphigus conjunctivae were treated for an extended period with massive doses of vitamin D. Both had conjunctival and oral lesions. No improvement was noted in either case.

Discussion

No etiologic significance can be attached to the chemical changes observed in pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vulgaris chronicus. In the first place, during the earliest part of the disease when there were only a few lesions present the chemical determinations usually showed normal values. Furthermore, 3 of the 4 patients who died of pemphigus had at the time of death abnormally high sodium concentrations and 3 had abnormally high calcium concentrations in the blood serum. Although the high values can be attributed to the treatment, the fact that they were encountered at the time of death excludes sodium or calcium deficiency as a primary factor in the cause of the disease. The reduction of the serum sodium, chloride, calcium and protein is therefore regarded as a secondary symptom produced by the disease. It is possible that the chemical changes are due to the loss of plasma through the cutaneous lesions and the resulting osmotic changes. Damage to the adrenal glands, as observed in 2 patients with pemphigus vulgaris acutus and reported in one of the previous communications,[1] may be a factor of importance in some cases.

The favorable results obtained by treatment with adrenocortical extract, dihydrotachysterol or massive doses of vitamin D in some cases of pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vulgaris chronicus are apparently based on the tendency of these drugs to correct the chemical changes that occur in these forms of pemphigus. Since the chemical changes are secondary symptoms produced by the disease, the treatment is regarded as merely symptomatic. Although its limitations are fully realized, it is believed that it may well be tried in patients with pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vulgaris chronicus, not only as a measure for correction but also as a means for prevention of the chemical changes. Whether or not treatment with dihydrotachysterol or massive doses of vitamin D is of any value in the early, bullous stage of pemphigus foliaceus is a question that only further investigation can decide.

Summary

Six types of pemphigus are recognized — pemphigus vulgaris acutus (Brocq's *pemphigus subaigu malin*), pemphigus vegetans, pemphigus vulgaris chronicus, pemphigus foliaceus, pemphigus erythematosus (Senear–Usher type of pemphigus) and pemphigus conjunctivae.

In pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vulgaris chronicus, the amount of sodium, chloride, calcium and protein in the blood serum was found to be reduced. These changes were more pronounced in pemphigus vulgaris acutus and pemphigus vegetans than in pemphigus vulgaris chronicus. The degree of reduction usually corresponded to the severity of the clinical condition and the amount of skin involved.

No etiologic significance can be attached to the chemical changes. They are regarded as a secondary symptom produced by the disease.

Thirty-two patients with pemphigus were treated with adrenocortical extract, dihydrotachysterol or massive doses of vitamin D. Encouraging results were obtained in several patients with pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vulgaris chronicus. The results of treatment in patients with pemphigus foliaceus, pemphigus erythematosus and pemphigus conjunctivae were in general disappointing.

The treatment tends to correct the reduction of sodium, chloride, calcium and protein encountered in such patients. Since it is believed that the chemical changes are secondary symptoms produced by the disease, the treatment is merely symptomatic.

References

1. Talbott, J. H., Lever, W. F., and Consolazio, W. V. Metabolic studies on patients with pemphigus. *J. Invest. Dermat.* **3**:31-68, 1940.
2. Lever, W. F., and Talbott, J. H. Action of dihydrotachysterol in chronic pemphigus. *Arch. Dermat. & Syph.* **43**:341-356, 1941.
3. *Idem.* Pemphigus: clinical analysis and follow-up study of sixty-two patients. *Arch. Dermat. & Syph.* **46**:348-357, 1942.
4. Thost, A. Schleimhautpemphigus. *Deutsche med. Wchnschr.* **45**: 477, 1919.
5. Serefis, S. Über die prognostische Bedeutung der Schleimhautveränderungen beim Pemphigus. *Dermat. Wchnschr.* **96**:145, 150, 1933.
6. Senear, F. E., and Usher, B. Unusual type of pemphigus: combining features of lupus erythematosus. *Arch. Dermat. & Syph.* **13**: 761-781, 1926.
7. Brocq, A. J. L. Schème des éruptions bulleuses: le pemphigus subaigu malin à bulles extensives, et faits connexes. *Ann. de dermat. et syph.* **7**:449-461, 1919.
8. Lever, W. F. Severe erythema multiforme: report of two cases of type ectodermosis erosiva pluriorificialis, with development of cicatricial conjunctivitis and keratitis in one case. *Arch. Dermat. & Syph.* **49**:47-56, 1944.

9. Lane, J. E., and Lambert, R. A. Subacute malignant pemphigus with extensive bullae. *Arch. Dermat. & Syph.* **4**:141, 1921.
10. Pelagatti, M. Pemfigo. Nota clinica. *Ateneo parmense*. September, 1929. P. I. (Abstr. in *Dermat. Wchnschr.* **91**:1135, 1930.)
11. Lever, W. F. Oral lesions in pemphigus. *Am. J. Orthodontics* (Oral Surg. Sect.) **28**:569-580, 1942.
12. Frühwald, R. *Pemphigus Vegetans*. 430 pp. Leipzig: L. Voss, 1915.
13. Gray, A. M. H. Pemphigus of Senear-Usher type. *Proc. Roy. Soc. Med.* **31**:871-874, 1938.
14. Shannon, J. A. Kidney. *Ann. Rev. Physiol.* **4**:297-328, 1942.
15. Albright, F., Bloomberg, E., Drake, T., and Sulkowitch, H. W. Comparison of effects of A. T. 10 (dihydrotachysterol) and vitamin D on calcium and phosphorus metabolism in hypoparathyroidism. *J. Clin. Investigation* **17**:317-329, 1938.
16. Talbott, J. H., and Lever, W. F. Action of dihydrotachysterol (A. T. 10) on concentration of serum sodium, protein and calcium. *J. Clin. Investigation* **19**:786, 1940.

MEDICAL PROGRESS

DISEASES OF THE VEINS

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VENOUS THROMBOSIS AND PULMONARY EMBOLISM

PATHOLOGISTS have long recognized the frequency of thrombosis in the deep veins of the lower legs. Only occasionally have impressive observations been reported; yet when post-mortem examinations have been made with the clinical problem in view, it has been discovered that following death from a great variety of causes, deep-venous thrombosis has been found below the knees in at least 25 per cent of all the subjects investigated. In some reports the percentage is much higher. A good example of a study of this sort, previously quoted in progress notes made by me in 1942, is that of Hunter, Sneeden, Robertson and Snyder.[1] They undertook to discover the percentage of venous thrombosis of the lower leg in patients from a charity hospital, from a state psychopathic institution and from two private hospitals, believing, very naturally, that the background of the patient and the nature of his illness might influence the frequency of the disease. Needless to say, they were looking for the quiet type, — the so-called "phlebothrombosis" — which is necessarily little noticed clinically and that is recognized today as the usual source of pulmonary embolism.

They found thrombi of various ages to be present in 52.7 per cent of the 351 unselected middle-aged and elderly patients who had been forced to bed for varying periods before death. They studied microscopically 209 pairs of soleus and gastrocnemius muscles. Inasmuch as pulmonary embolism had been responsible for only 3.1 per cent of all the deaths in their series, it is evident that much of the thrombosis had either healed or was a terminal manifestation, not having advanced upward beyond the lower legs. This is in accordance with still earlier pathological observations of Rössle,[2] who found what may be described as terminal thrombosis in 25 per cent of all cases, and of Neumann,[3] who reported isolated venous thrombosis confined to the parts below the knees in 29 per cent of the bodies investigated. It appears that in the study of Hunter and his associates the percentage of lower-leg thrombosis in the various hospitals was 59 per cent in the charity hospital, 49 per cent in the state psychopathic institution and 40 to 42 per cent in the two private hospitals. From such figures as these one is justified in concluding that confinement to bed, whatever its cause, tends to lead to thrombosis in the veins of the legs and that the more enfeebled patients show a higher percentage of disease than do the better preserved ones. Indeed, it has been too little recognized that serious illnesses, including those of the heart itself, are frequently complicated by quiet thrombosis and fairly often terminated by pulmonary embolism. Rössle,[2] in the study of his relatively small series, remarks that the death of the patient cuts off the development of many low processes that would otherwise have spread upward into the femoral vein. One need not follow this line further, but need only recognize that here is a background against which observations made during life may be interpreted.

An important aspect of deep venous thrombosis is the causal relation of trauma, in the broad sense. One must think of surgical operations — unfortunately — in this connection, especially in patients suffering from cancer or other debilitating diseases, but fracture of any bone of the lower limbs, including those of the feet, whatever the form of fixation used, must be regarded as almost as important a cause of thrombosis and pulmonary embolism. My[4] first experiences with actual or threatened embolism arose from metatarsal fractures in vigorous middle-aged persons. Just where post-partum thrombosis belongs in the picture is difficult to say. There is reason, of course, to suspect an entirely pelvic origin, but since there is nothing about a "milk leg" that is essentially different from any other thrombophlebitis, the lower leg should, for the moment, be regarded as its chief source.

How does such thrombosis arise? Wright[5, 6] offers a reasonable explanation for what may be at least

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a contributing factor. He finds that the blood-platelet count rises following childbirth and surgical operations. The rise begins on the fourth day and reaches its maximum on the twelfth, falling back to normal on the twenty-first. There is a rough correspondence here with the clinical onset of thrombosis. But platelets do more than multiply. According to Wright, they become "sticky." Adhesiveness increases as the thrombocytes grow in number and is attributed to the quality of the platelets rather than to a change in the serum. Such phenomena have not been invoked in explanation of nontraumatic forms of venous thrombosis; that is, those that so frequently complicate serious illness, as well as the less common ones of active life. They may not perhaps be of great significance and they are certainly not fundamental. Even if invoked to explain postoperative thrombosis, they can hardly apply before the fourth day; and Newburger,[7]* in a recent collective review of early postoperative walking, notes that since those physicians who got their patients out of bed on the third day still encountered thrombosis and embolism, thrombosis must often begin earlier — a suggestion in which I concur. Probably the moment of onset varies considerably and one must continue to regard life in bed, the reclining position, abdominal distention, enfeeblement of the circulation and elevation of venous pressure in the lower limbs, perhaps combined with muscular relaxation and atrophy of the legs, as of first importance.

A recent development, stimulated by White's[8] observations on patients suffering from, or thought to be suffering from, cardiac or pulmonary disease, is the realization that quiet thrombosis may take place not only in persons already incapacitated by a cardiac disorder of some sort but in others apparently leading an active and sufficiently normal life. Such persons may even be young, — that is, in their teens, — although pulmonary embolism in the first four or five decades is unusual. That fatal embolism seldom occurs before the age of fifty was brought out by Welch and Faxon[9] in their study of patients, mainly postoperative, at the Massachusetts General Hospital in 1941. I myself,[10] dealing with a necessarily small ambulatory group, some of whom, because of repeated nonfatal embolism, had been falsely accused of suffering from angina or disease of their coronary arteries, have found the same thing to be true. Quiet venous thrombosis in the deep veins of the lower legs may take place at any age, although increasing in frequency with the years, but a fatal accident before the fiftieth year is rare. It is remarkable how often pulmonary embolism may occur and recur in ambulatory patients and how likely such persons are to be suspected of cardiac or pulmonary ailments rather than of embolism from an unnoticed deep thrombosis in the lower legs. It is not even necessary that the patient should have suffered from an old thrombophlebitis now canalized. The veins of the legs may previously have been, so far as one can learn, entirely normal, giving no excuse whatever for a thrombotic process. As will appear later, the patient of fifty or over who suffers from an arterial deficiency is probably more liable to venous thrombosis, and perhaps embolism as well, than is the normal person. The thrombosis of active life does not, of course, crop up nearly so often as that of postoperative, post-traumatic and post-partum states, to say nothing of generalized circulatory failure, but is brought up here because physicians and laity alike are only too apt to deny the possibility of its occurrence.

*The review, by the way, shows that early postoperative walking is of advantage in more ways than one. Even if it does not do away with postoperative thrombosis and embolism, it appears to diminish its incidence rather than otherwise.

Course of Lower-Leg Venous Thrombosis

In the recent paper to which allusion has just been made[10] and in a paper presently to be published,[11] I call attention to the various courses that may be pursued by a venous thrombosis beginning in the lower leg or foot. I point out that the process may remain local without causing pulmonary embolism, that it may form a dangerous propagating thrombus that spreads up into the femoral vein and is the usual cause of the most serious sort of embolism, that it may extend upward in a more or less adherent form, partly filling the femoral and iliac veins, a rather prolonged disease with which a complicating thrombosis of the deep muscular veins of the thigh is likely to be associated, and which often ends fatally or that it may extend upward in a quiet form until, for reasons of which nothing is as yet known, it acquires an inflammatory element, to plug completely the femoral and iliac veins, causing swelling of the entire leg and the familiar picture of phlegmasia alba dolens. In this fourth course, the commonest, perhaps, in past experience, a nonsuppurative infection appears to be the added feature, leading to perivascular involvement that affects the arterial wall as well as the various sorts of nerves surrounding the great vessels in the region of the groin and pelvis. As a result of this perivascular inflammation, there occurs not only some degree of local contraction of the companion artery but by what seems to be a reflex mechanism, a generalized constriction of the vessels of the entire limb. This condition has been called "thrombophlebitis" in contradistinction to the quiet disease or, if one likes, the quiet preliminary stage of this same process, dubbed by Ochsner and DeBakey[12] "phlebothrombosis."

Various opinions have been expressed concerning the importance of a distinction between phlebothrombosis and thrombophlebitis. In a recent paper, Ochsner and DeBakey[13] make no attempt to trace the connection between them, but dwell very properly on the necessity of treating the two sorts dif-

ferently. Welch and Faxon[9] seem to think that since the diseases merge into one another, the distinction between them is not of fundamental importance. All agree, however, that from the solid, inflammatory thrombus, pulmonary emboli are very unlikely to be detached, whereas with the quiet, nonobstructive one, much more like a soft clot, embolism is always threatened. Ochsner and DeBakey point out the wisdom of relaxing the various sorts of vasoconstriction in thrombophlebitis by a lumbar sympathetic block, and what may be called "the Boston school," including Welch and Faxon,[9] Welch, Faxon and McGahey,[14] Allen, Linton and Donaldson,[15] Fine and Sears,[16] Fine, Frank and Starr,[17] myself and others, has long advocated, for the quiet phlebothrombosis, division of the principal vein of the limb or limbs affected, with the idea of halting the process and of preventing pulmonary embolism. Hence the importance of distinguishing between the two types — or, it may be, stages — is obvious.

Diagnosis

In their recent paper, Allen, Linton and Donaldson[15] make the point that if one could see a four-hourly temperature chart of every patient subject to the possibility of venous thrombosis in the legs, there would be evident, as the earliest sign of embolic detachment, a rise of pulse rate and temperature. I myself believe that entirely apart from gross embolism, a soft propagating thrombus often gives off small fragments that, without causing outspoken signs, disturb the pulmonary circulation, causing an increased respiratory and cardiac rate. One notices, for instance, after effective interruption of the principal vein or veins proximal to the thrombus, an immediate easing of the clinical situation, much more definite than might come, for example, through relief of the patient's anxiety, if such were present. Thrombosis itself need occasion no rise whatever, and there is often an interval of hours or days between the rise and the first thoracic symptoms of *gross* embolism. The trouble with this observation is that it is usually made in retrospect, and of course there are other causes of an elevation in the pulse rate and temperature curve besides the onset of embolism. Observation of the chart should be regarded as of the very first importance, however, and, along with the various physical signs in the legs themselves, is extraordinarily helpful. DeTakats[18] takes this view, saying that a slight rise of temperature and a persistently elevated pulse rate, without apparent cause, after the fourth or fifth postoperative day should make one seek other signs of latent thrombosis. Among other things, he is interested in the skin temperature and soreness to touch of the sole of the foot. Allen and his associates[15] mention in the order of their frequency a number of positive findings. In their series, some degree of swelling was found in 67 per cent of the 237 cases examined, tenderness was found in 61 per cent of 231 cases investigated with that finding in view, and in 139 cases examined for what they called "Homans's sign," — I prefer to call it the dorsiflexion sign, — this was found to be present in 42 per cent. I regard this dorsiflexion sign as having a greater degree of importance than would be judged from this analysis. Actually, dorsiflexion of the feet is intended to bring out, on the side of the venous thrombosis, some degree of irritability of the posterior muscles, the soleus and gastrocnemius. Discomfort need have no part in this reaction. Dorsiflexion may be less complete in response to an equal degree of upward pressure on the affected side as compared with the normal, or the patient may involuntarily flex the knee as the forefoot is forced upward, to release the tension on the posterior muscles. If one looks on the dorsiflexion sign as evidence of even the faintest irritability of the posterior muscles, — the early stage of the thrombosis occurring within and about them, — the sign will probably be found present more frequently than either tenderness or swelling.

Pulmonary embolism. As Allen and his associates note, pulmonary embolism is the first evidence of deep venous thrombosis in the lower limbs in a considerable proportion of cases — 41 per cent in their series. This does not mean that signs in the legs may not have been present but that none have been observed. It is true, however, that in a surprising number of persons some sort of thoracic distress or pain, or breathlessness, or cough gives the only hint that a quiet thrombosis in the legs is going on. This is in accordance with the general rule recognized by all those familiar with this subject; namely, that the more silent and less inflammatory the thrombosis in the lower limbs, the likelier is the process to cause pulmonary embolism. An outspoken thrombophlebitis, being an adherent, occluding process, rarely occasions any such accident. The quietest sort of thrombosis may occupy only a small stretch of vein among the calf muscles yet give rise to a long, hanging, potentially fatal thrombus.

Although it is not properly a subject of these notes, attention is called here to the importance of the electrocardiogram in the diagnosis of pulmonary embolism. As early as 1935, McGinn and White[19] described cor pulmonale and its characteristic physical and electrocardiographic signs. In a recent communication, Murnaghan, McGinn and White[20] develop further the whole subject of the electrocardiographic diagnosis of pulmonary embolism, citing a number of clinical reports. Among their series of 10 cases were 3 of pulmonary embolism following bone injuries in women over sixty, 3 of postoperative embolism, 2 of these occurring in the third decade, and 3 in which the patients presented pulmonary symptoms from the beginning of their illness. Nine of these 10 patients had two or more attacks of infarction, the tenth only one. In 3 cases,

the electrocardiogram gave the first suggestive laboratory evidence of the correct diagnosis; in the rest it confirmed a clinical diagnosis. From the Mayo Clinic comes another report by Currens[21] dealing with the importance of the electrocardiogram in the diagnosis of pulmonary embolism. This observer holds that the strain on the right ventricle seems to be the dominant factor in causing the electrocardiographic changes.

Phlebography. This diagnostic aid has proved, on the whole, disappointing. It has been advocated as a trustworthy means of making an early diagnosis (following the lead of dos Santos[22] and of Bauer[23]) by Welch, Faxon and McGahey,[14] by Starr, Frank and Fine[24] and, more recently, by DeBakey, Schroeder and Ochsner.[25] On the other hand, Allen, Linton and Donaldson,[15] reversing the opinion expressed earlier by the Massachusetts General Hospital group, find it rather untrustworthy, for, as they say, phlebograms are difficult to interpret and may be misleading. In this latter view, I join. The phlebogram, if positive, is sometimes astonishingly accurate and defines the thrombus and its extent in a way that no other diagnostic procedure can do, but in too many cases it leaves the diagnosis unproved, particularly in cases in which it is imperative that further pulmonary embolism should be prevented, and sometimes it suggests a positive diagnosis of thrombosis when no such process is present. In other words, the filling of the deep veins of the lower leg by a solution opaque to the x-ray is a somewhat uncertain procedure. I have found it most useful and reliable in giving information concerning a past or present thrombosis in the femoral vein, that is, in the deep vein above the knee. In the case of a rather chronic process, it may be very helpful to know whether to section the femoral vein proximal to the thrombus or whether one must go higher and expose the common iliac or the vena cava, but this is by no means making a diagnosis in the early or doubtful case; it is merely a refinement of a diagnosis already made.

Treatment

Heparin and dicoumarol. When one reads the publications of those accustomed to deal with deep venous thrombosis and pulmonary embolism by operative means, one is hardly made aware that such a treatment as the administration of heparin or dicoumarol exists. Yet when one reads Murray's[26] statement that, following an initial pulmonary infarction, not one of his 46 heparinized patients suffered a fatal pulmonary embolism, one must agree that there is virtue in this method. A recent report by Evans,[27] from the Lahey Clinic, on a short series of cases in which he depended mainly on dicoumarol (with which he sometimes combined heparin) presents certain advantages for this line of treatment, although it must be admitted that the death of 2 patients in 56* from hemorrhage is disconcerting, to say the least. So far as Boston is concerned, Evans appears to be a voice crying in the wilderness, but he receives support from other parts of the country. A recent editorial in the *Journal of the American Medical Association*[28] comments favorably regarding the prevention of venous thrombosis by the administration of dicoumarol to the experimental animal.

What troubles me in attempting to assay the value of the heparin-dicoumarol treatment is that in the reports I have so far studied, *postoperative* thrombosis has been, practically speaking, the only sort on which a trial has been made, thrombophlebitis has been lumped together with the quiet, dangerous type, — 13 out of Evans's 17 postoperative cases were of the inflammatory, obstructive sort, whereas only 4 represented phlebothrombosis — and, moreover, no parallel series of operative versus drug therapy in any large clinic is known to me to have been undertaken. Actually, the great field of thrombosis and embolism in those confined to bed by cardiac, pulmonary and other serious diseases has hardly been touched. These are fundamental omissions. It only appears, so far, that heparin is capable, if properly administered, of preventing the onset of thrombosis; that is, if given after operation, thrombosis and embolism are unlikely to occur. This, of course, is good, and if heparin were not so expensive and its administration were not so difficult and time-consuming a matter, heparinization, as a prophylactic, at least, could be freely recommended. So far as heparin alone is concerned, one cannot go much farther. Many surgeons believe that if given carefully, when pulmonary embolism has already taken place, it will halt embolism during the actual period of its administration but will not prevent a fatal recurrence following withdrawal of the drug.

Dicoumarol, in contrast with heparin, is cheap, is given by mouth and, by profoundly lowering the prothrombin level in the blood, prevents thrombosis. Thus it has certain advantages. But whereas heparin acts to prevent both clotting and adhesiveness of the thrombocyte (a basic part of thrombosis) only during its administration, and rapidly leaves the blood stream as soon as no more is introduced, dicoumarol continues to hold down the prothrombin level for many days after even moderate doses. Yet it does not delay coagulation. It may even cause serious or fatal bleeding while not prolonging the clotting time at all, and its dangerous effect can only be combated by the introduction of prothrombin through abundant transfusion of whole blood. For such reasons, Rhoads, Walker and Panzer[29] believe that dicoumarol and heparin should be looked on as complementary drugs and should be given together — dicoumarol by mouth and

*Actually only 46 cases of thrombosis or with a history of venous thrombosis were treated with dicoumarol and no deaths from hemorrhage occurred among them.

heparin for the most part intramuscularly. They find that in the "coumarinized" patient, the effect of a single intravenous injection of heparin is to sustain a prolonged clotting time for even as long as twenty-four hours. Thus heparin need not be given continuously, and intramuscular doses* can be substituted. Following an initial pulmonary embolism, they give heparin intravenously for a few hours. In the meantime, dicoumarol is started by mouth and, after the intravenous heparin has taken effect, intramuscular injection of the drug is begun. They indicate that two 5-cc. doses of heparin each day are sufficient. Three hundred milligrams of dicoumarol is given by mouth the first day, 200 mg. the second, and thereafter the dosage is governed by the prothrombin level. To use this system safely, prothrombin levels must be determined daily and the clotting time measured twice daily, clearly a matter requiring adequate and intelligent assistance, by no means foolproof. Their observations have been made experimentally and on a series of 15 patients without accident.

Barker, Allen and Waugh,[32] from the Mayo Clinic, treated a series of 497 cases, all postoperative. Their principal groups included those who had already survived a pulmonary embolism and those who had had postoperative "thrombophlebitis." They used dicoumarol principally. They made no attempt to distinguish phlebothrombosis from thrombophlebitis. They do not state how long their patients were followed (to detect late embolism after withdrawal of the drug). They had 47 cases — 10 per cent — of more or less serious bleeding and 1 fatal hemorrhage. Nevertheless they believe that they reduced embolism far below expectation according to the system of statistics used, and conclude:

> Adequate elevation of prothrombin time by means of administration of dicoumarol by mouth to postoperative patients is apparently effective in preventing postoperative thrombosis and pulmonary embolism. A plan of administration whereby 300 mg. are given on the first day, 200 mg. on the second day and 200 mg. on each subsequent day that the prothrombin time is less than thirty-five seconds (normal, eighteen to twenty-two seconds) has proved satisfactory. At present it is unwise to give dicoumarol unless the prothrombin time can be determined accurately each day. There is some risk of bleeding in postoperative cases when dicoumarol is given, but this risk is comparatively small. If hemorrhage occurs, it can be controlled by transfusion of freshly drawn blood.

In an editorial, DeBakey[33] expresses the opinion that at the present time the postoperative use of anticoagulants is too apt to cause hemorrhage and that proximal ligation of the thrombosed vein is to be preferred. He voices distrust of the type of statistics employed by Barker and his associates. I believe, however, that it would not be at all surprising if the combined administration of heparin and dicoumarol should prove exceedingly helpful when all known safeguards are used, and especially if discrimination is exercised in the selection of cases. DeTakats[34] has put forward a test for heparin tolerance, that is, the reaction of the patient's coagulation time to a standard intravenous dose of heparin. He finds that some patients are resistant to heparin; that is, they are thrombophilic, especially in the early postoperative period, following cardiovascular accidents and in Buerger's disease. Others are heparin-sensitive. His observations on various methods of giving heparin should be studied, and he recommends frequent tests, by the capillary glass-tube method, of the coagulation time. He advocates the combined use of heparin and dicoumarol.

Surgical treatment. Section or ligation of veins as a means of therapy seems to have been advocated chiefly by Boston surgeons. The recent publication of Allen, Linton and Donaldson[15] gives as fair a picture of indications and results as is at present available. The tendency is to use exploration of the superficial or common femoral vein for all early cases in which quiet thrombosis has been diagnosed, whether or not embolism has occurred, and to suck the thrombus out of the vein proximal to the groin whenever it is encountered. Allen and his associates, although constantly trying to improve their "diagnostic acumen," believe that in their attempt to cut off all possible sources of pulmonary embolism they will inevitably perform some unnecessary operations. I[10] have employed similar methods but have attempted to distinguish the more chronic and recurrent forms of thrombosis marked by extension of the quiet process into the iliac veins. For such cases I have employed section of the common iliac vein, which I advocate, and in a paper now in publication I[11] debate the pros and cons of this higher operation and the indication for ligation of the lower vena cava, a procedure that surely has a limited though definite field of usefulness. In this connection, it is of considerable interest that Shackelford and Whitehill[35] report the successful section of the left common iliac vein in a soldier, twenty-eight years of age, who had suffered repeated pulmonary embolism during active military service. The patient had malaria, but the connection of the disease with venous thrombosis in the lower limb was probably not important.

For the technic of the various operative procedures to be employed one may consult the writings of Welch and Faxon,[9] Welch, Faxon and McGahey,[14] Allen, Linton and Donaldson,[15] Fine and Sears,[16] Homans[36] and others, but there are problems as yet unsolved. For example, if one is making an exploration of the vessel at the groin and finds a palpably thrombosed but presumably not fully ob-

*Very likely further satisfactory intramuscular or subcutaneous means of administering heparin will be developed. Recently a method has been reported from the Mayo Clinic by Bryson and Code,[30] who administered subcutaneously a suspension of powdered heparin in a beeswax-sesame oil mixture and found that a satisfactory and prolonged coagulation time could be secured in the experimental animal. The method has even been tried out on several patients. Bryson and Code allude to previous observations of Loewe, Rosenblatt and Lederer,[31] who gave heparin in a mixture of gelatin, glacial acetic acid, glucose, a vasoconstrictor drug and water, reporting satisfactory observations on rabbits. It will be interesting to hear further from such attempts, which sound decidedly promising.

structed femoral vein, is it better to suck out all removable thrombus and section the vein, or shall one leave the vein alone and, closing the wound, undertake a common iliac division or even ligation of the vena cava? This matter is urgent because one may fail to remove all thrombus by suction, and subsequently, further detachment of material from some part of the iliac veins may occur. Another problem is the question whether, in such a case as has just been postulated, heparinization or a combined administration of heparin and dicoumarol shall follow the operation. Still another uncertainty is whether bilateral femoral division shall be performed in all cases of serious pulmonary embolism even though only one limb clearly exhibits signs of thrombosis. Finally, in the case of a breathless patient whose pulmonary arteries are evidently full of emboli and whose lower limbs show no convincing signs of thrombosis, shall one undertake the risk of attempting a division of the vena cava, or shall one expose both femoral vessels and suck out the soft thrombus, or shall one abandon operative surgery altogether and attempt to cure the patient by the combined use of heparin and dicoumarol? Settlement of these matters is most urgent in the case of extremely ill medical patients, especially those suffering from cardiac disease, for which a wide-awake medical service in any large hospital is likely in these days to seek treatment. Embolism may already have occurred without any positive signs of thrombosis in the legs, or in the absence of any signs of embolism, the legs themselves may be suspected of harboring a deep thrombosis. In a two-month period (February and March, 1944) at the Peter Bent Brigham Hospital, twelve vein interruptions were performed on medical cases as compared with six surgical ones. Most were femoral sections, but two ligations of the vena cava were made. The higher operations are most decisive, but are they too dangerous? If a general anesthetic seems to carry too great a risk, division of the vena cava can perhaps be performed under a right-sided paravertebral procaine block. Doubtless, the patient's economic situation, the operator's skill and the familiarity of all concerned with the various methods of treatment will be found to be controlling factors in standardizing treatment.

Ligation of the vena cava has long been practiced sporadically by gynecologists and obstetricians. A recent account has been given by Collins, Jones and Nelson.[37] Of course, the thromboses beginning in the pelvis, and especially those of a septic sort following uterine infection, require section of the ovarian veins as well as of the vena cava itself and therefore call for a transperitoneal operation. It appears that such a procedure is somewhat different in its effect from division of the vena cava alone in the case of thrombosis beginning in the legs, and the results of the operations performed because of thrombosis complicating pelvic sepsis should not be used as guides in interpreting the after-effect of extraperitoneal ligations of the vena cava for phlebothrombosis of the lower leg. Undoubtedly my experience with section or ligation of the common iliac vein indicates that the venous return from the lower limb following this operation is much more satisfactory than that following division of the femoral vein. The same is not quite true of division of the lower vena cava, for in that case shunting of the blood from one side of the pelvis to the other is not available. It is proper to say, however, that in the observation of the dozen or so cases of division of the vena cava of which I have knowledge (unpublished observations), the subsequent venous return from the legs has been remarkably satisfactory and no serious aftereffects have as yet been observed.

It will be noted that nothing has been said of the treatment of thrombophlebitis (phlegmasia alba dolens) by lumbar sympathetic procaine block. Actually no new information as the results of this valuable procedure has appeared within the last two years.

Venous Thrombosis Associated with Arterial Obstruction

The association of venous thrombosis with arterial obstruction of various sorts, particularly in the lower limbs, has received insufficient attention. It would be rather trite to observe that there is such a disease as thromboangiitis obliterans, a disease in which venous and arterial thromboses are intimately associated. It is not even known, for instance, whether the primary process lies in one sort of vessel or the other. One sees, however, occasional cases in which arterial stoppage is obviously primary, yet with which there is so much venous stasis as to suggest that venous has become associated with arterial obstruction. I have also encountered pulmonary embolism in combination with some rather chronic arterial deficiencies. In this connection, an unusual paper was published some years ago by Cornil, Mosinger and Audier.[38] After calling attention to the association of phlebitis with arteritis in Buerger's disease and pointing out that arterial symptoms are frequently present with thrombophlebitis, they undertake to explain how thrombosis may be communicated from large artery to companion vein or from companion vein to large artery. They believe that with perhaps 40 per cent of arterial closures there is an associated venous thrombosis. In explanation, they show that the media and adventitia of the veins contain capillary vessels, supposedly lymphatic, which they find present only in the adventitia of the arteries. An inflammatory reaction starting within the arterio-venous sheath may extend, therefore, in a lateral direction and even longitudinally, the subsequent lateral extension producing results at a distance from the original lesion. When an inflammation

reaches the vein from the artery, it may occupy both the adventitia and the media, a phenomenon that would explain the frequent thrombosis of large veins associated with arterial disease. But when an inflammatory process is communicated from vein to artery, it involves only the adventitia and so causes spasm of the arterial wall rather than thrombosis. All such reactions depend on the enclosure of large arteries and veins in a common sheath within which are included the anastomosing lymphatic vessels.

Several communications are available relating to the presence of venous thrombosis and even pulmonary embolism in obstructive arterial disease. Veal[39] finds it worth while, in thigh amputations for gangrene of arterial origin, to ligate the femoral vein before amputation is performed. He believes that by so doing he prevents considerable pulmonary embolism. Atlas[40] describes a rather complicated case of thrombosis and embolism following amputation in which he was obligated to divide the vena cava, and I (unpublished data) have noticed, in connection with an unexplained arterial embolism that had caused gangrene of the lower leg, an associated thrombosis of the femoral vein obviously secondary to the lodgment of the embolus. This was discovered in an exploration of the femoral vessels at the groin in a search for the cause of the gangrene. Resection of that part of the artery containing the embolus, and of the companion vein as well, was employed. Such observations as these offer an explanation of the obvious venous engorgement associated with some fairly acute and outspoken obstructions in the femoral artery and perhaps account for the heat that is present in the feet of some of these patients, a heat obviously not due to infection and rather difficult to explain solely on a basis of a sudden cutting down of the arterial stream. Possibly, venous thrombosis associated with a sudden arterial occlusion is a useful natural provision, raising the venous pressure in the periphery of the limb and so actually improving the nutrition of the peripheral parts. Occasionally, of course, the associated venous thrombosis is a quiet one, almost necessarily overshadowed by the arterial occlusion, and if only partly obstructive is of the type that causes pulmonary embolism.

Venous pressure and the arterial circulation. Although not strictly relevant to the subject of diseases of the veins, the reaction of local venous pressure in a limb on the arterial circulation is an important matter and has recently received a good deal of discussion. It will be recalled that for some years intermittent venous occlusion has been recommended as a means of establishing a collateral circulation, in connection with various sorts of arterial obstruction and deficiency. Linton, Morrison, Ulfelder, and Libby[41] demonstrated to their own satisfaction in the experimental animal that occlusion of the principal vein of a limb induced increased arterial pressure in that limb, and that there were relations between the point at which the occlusion was made, and the length of time it was maintained, with the degree to which arterial pressure was elevated. The whole matter is related to the circulatory balance, which has long been regarded as of fundamental importance when large arteries must be sacrificed. The observations of these writers were consistent with the practice of dividing the companion vein at the same level as the arterial section or higher. More recently, Friedland, Hunt and Wilkins[42] have measured the arterial flow in the extremities of human beings with and without the venous congestion produced by inflating a blood-pressure cuff on the proximal part of the limb. They tested the flow by various methods and found that it was not increased in the limbs during the rise of venous pressure but on the contrary was usually decreased. This subject comes up acutely, of course, in these war times when a wounded limb is on the borderline of gangrene as a result of a serious arterial injury. Ligation of the companion vein, hitherto regarded as essential, may prove to be less important than intermittent depression of the level of the wounded limb, the idea being to secure some degree of venous engorgement without bringing on a harmful edema. "Intermittent venous occlusion" in treating various sorts of arterial deficiency in the lower limbs is still on trial.

Thrombosis in Various Veins of the Body

Idiopathic recurrent thrombophlebitis. Bucy and Lesemann[43] report a remarkable case of recurrent thrombophlebitis in which the condition was exhibited over a period of fifteen years in various parts of the body. The disease had shown itself, previous to the most recent episode, in both legs and one arm. Finally it involved some of the cerebral cortical veins and the retinal veins of the right eye. Associated with this attack was an acute subdural hemorrhage, requiring evacuation of the hematoma. The patient recovered. The literature is summarized.

Mesenteric thrombosis treated with heparin. Luke[44] reports a case of venous mesenteric thrombosis in a soldier of forty-two. The history and physical examination were typical. Exploratory operation disclosed thrombosis in the mesenteric veins serving about 135 cm. of small bowel. The intestine appeared barely viable. The patient recovered under heparinization.

Septic thrombosis of cavernous sinus. Schall[45] reports 3 patients suffering from cavernous sinus thrombosis of the anterior type, with staphylococcal bacteremia, successfully treated by sulfathiazole and heparin. Sulfathiazole was given in sufficient dosage to maintain a blood level of 5 mg. per 100 cc. and was continued for a long period after the administration of heparin was discontinued. Schall discusses the theoretical value of this combination, as suggested by Lyons,[46] and the possible use of

sulfonamides other than sulfathiazole. Apparently the principle of combining heparin with a sulfonamide is a sound one.

Varicose Veins

It is to be observed that the tendency evident in previous progress notes on varicose veins has continued. Papers are appearing describing technics for sclerosing injection, but on the whole the study of etiologic factors and of the interrelation of varicose veins and venous pressures has been more in evidence. In 1942, favorable comment was made on Adams's[47] communication discussing pressure in varicose veins as compared with normal veins of the lower extremities. Adams showed that, in the standing position, pressure in both sorts of vessels was equally due to gravity alone, unless coughing or straining occurred. Then, pressure in the valveless varicose veins rose even to arterial heights, whereas in the well-valved femoral system this extra rise failed to occur. One corollary of his work was to belittle the value of elaborate tests for incompetent communicating veins, "blowouts" and so on, since adequate high ligation prevents the rise of pressure in varicose veins below the interruption, due to straining, and pressure in such veins, which are connected only with the valved femoral system, continues to represent the effect of gravity and of gravity alone, whether or not communicating veins are also interrupted. Another significant communication was that of Veal and Hussey,[48] who found elevated pressures in the popliteal veins of pregnant women, showing how functional incompetence of valves explains the well-known causal relation between pregnancy and varicosity. In this connection, it will be noticed that Adams advised the addition of straining to the Trendelenburg test, which ordinarily records the effect of gravity only, for by that means the actual clinical competence of the varicose veins to forward blood and resist high back pressure can be determined.

Etiology. Eger and Casper[49] believe that since there are no valves in the vena cava and common iliac veins, it is the role of such valves as are present in the external iliac veins to support, proximal to the legs, the long column of venous blood. Actually, these valves are inconstant, and their absence imposes a greater than natural burden on those in the femoral system below. If valves in the common femoral vein are also wanting, the saphenous, as well, is directly exposed to high back pressures. In 7.9 per cent of their cadavers, Eger and Casper found a bilateral lack of valves above the orifice of the great saphenous, and in 35.8 per cent absence of valves on one side or the other. Only one valve is likely to be present in any case above the great saphenous. There was no valve on the right in 10.4 per cent and on the left in 18.5 per cent. They conclude that if lack of valves is the etiologic factor, varicosities should develop unilaterally in 29 per cent and bilaterally in 8 per cent of all persons. The left leg should show varicosity twice as often as the right. Another possible etiologic factor is an obstructive anomaly at the mouth of the left common iliac vein, to which attention is called by Krumbhaar and Ehrich.[50] This they found present in 30 per cent of 280 autopsies.

Pathologic physiology of varicosity. Chapman and Asmussen[51] bring up a subject as to which I have always been curious. I have expected to meet sometime a patient suffering from extensive varicosity who experienced faintness on standing up, owing to the rapid downpouring of blood into capacious, valveless veins. Actually I have never encountered this phenomenon, but Chapman and Asmussen go at the problem in a more scientific way. Starting with the fact that even normal persons are likely to accumulate in their lower limbs some 500 cc. of blood when standing still (over and above that which is present in the horizontal position), and recognizing the diminished output of the heart that has been observed to result, they have investigated some of the logical effects of the even greater downpour of blood into greatly dilated varicose veins. They find that, as compared with normal persons, those having large varices suffer a fall of cardiac output four times as great, a greater lowering of systolic blood pressure and a more marked increase in the pulse rate. After high interruption of the varicose veins, these tendencies are for the most part corrected. Patients suffering from shortness of breath, dizzy spells and faintness are greatly relieved. It is to be noted, however, that not all patients in whom the cardiac output is lowered excessively by the assumption of the upright position make any actual complaints. It appears therefore that only those on the borderline of cardiac incompetence are consciously suffering from the pooling of their blood in varicose veins. The authors note also an increase in blood volume in the varicose patient.

Venous pressure in the presence of varices has also been studied by Mayerson, Long and Giles.[52] Aware of the investigations of both Adams and the authors just quoted, they reason that since the vascular bed, in the presence of varicosity, is greatly enlarged, there must be a concomitant increase in blood volume similar to that of hyperthyroidism, cardiac disease and arteriovenous fistula. Thus, when the varicose patient assumes the horizontal position, his vessels contain more blood than he needs and consequently venous pressure rises. They show this high pressure to be present in the arms as well as the legs in their recumbent patients.

Such considerations as these bring up the rather interesting point whether high ligation without actual obliteration of varicose veins does for the borderline case all that might be accomplished in the way of reducing the capacity of the vascular bed. Partly with this point in mind, I carry out a low-

high division of varicose veins (at the knee and groin) and make a retrograde injection into the veins of the thigh, holding that veins closed at both ends are most likely to be obliterated by sclerosing solutions. I have been opposed to similar injections into the veins below the knee, believing that anything but small doses of substances like quinine and urethane or sodium morrhuate exposes the patient to the possibility of a considerable inflow of the sclerosing solution into the deep veins, with a possible risk of deep thrombosis, for the communicating veins are much more abundant below than above the knees and offer more direct connections between the superficial and deep veins. Atlas[53] has recently discussed this matter. He is aware of 5 cases in which retrograde injection of a sclerosing solution into the distal portion of the saphenous vein has been followed by thrombosis of the deep veins of the thigh. Two of these patients died from pulmonary embolism. Although Atlas is inclined to believe that the inflow of the sclerosing solution was into the deep veins of the thigh, it seems more likely that the deep thrombosis was set up below the knee, where it is far likelier in any case to begin. In these days when injections into the varicose saphenous system are recommended by introducing a small catheter from above (Pratt[54]), by way of a needle into a vein of the lower leg while the limb is in the elevated position (Bellis and Churney[55]) and by retrograde injection into the distal stump of the great saphenous, divided in the lower thigh (Pearce[56]), I am inclined to call attention to the danger of thrombosis and embolism following such procedures. A careful follow-up of patients so treated might be of considerable interest.

Evaluation of treatment. This has always been difficult, and a report of Larson and Smith[57] from the Mayo Clinic is of considerable interest. Among 395 surgical cases, 367 were treated by high ligation, division and injection of the great saphenous trunk. In the remaining 28 cases, incompetency of the lesser saphenous vein was independent of disease of the great saphenous system and was separately treated. After speaking of various tests to distinguish the two types of varicosity, the authors remark that the importance of the lesser saphenous system has been underemphasized. They believe that, if incompetency of this vein is established, it will often be unnecessary to perform the more extensive searches for, and ligations of, the "blowouts" advocated by various surgeons. I have long believed that of all the incompetent connections, below the groin, between the superficial and deep veins, the lesser saphenous is the only one to which much attention ought to be paid, and I heartily endorse this statement of Larson and Smith. Among their other observations, they speak particularly of edema and aching pain as symptoms that drive patients to seek operative treatment. Sixty-seven per cent of their patients presented these signs. Forty-six per cent complained of a feeling of heaviness and stiffness, and 41 per cent noticed nocturnal cramps in the calf or thigh. Their brief presentation is well worth studying. It is to be hoped that others will present reflections on varicose veins and their symptoms with equal brevity and fairness. A clinic sometime must make a follow-up study of those patients who present clean-cut symptoms to discover whether or not modern treatment cures them, without regard to the presence or absence of such dilated veins as may remain.

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References

1. Hunter, W. C., Sneeden, V. D., Robertson, T. D., and Snyder, G. A. C. Thrombosis of deep veins of leg: its clinical significance as exemplified in 351 autopsies. *Arch. Int. Med.* **68**:1-17, 1941.
2. Rössle, R. Über die Bedeutung und die Entstehung der Wadenvenenthrombosen. *Virchows Arch. f. path. Anat.* **300**:180-189, 1937.
3. Neumann, R. Ursprungszentren und Entwicklungsformen der Beinthrombose. *Virchows Arch. f. path. Anat.* **301**:708-735, 1938.
4. Homans, J. Thrombosis of deep veins of lower leg, causing pulmonary embolism. *New Eng. J. Med.* **211**:993-997, 1934.
5. Wright, H. P. Adhesiveness of blood platelets in normal subjects with varying concentrations of anti-coagulants. *J. Path. & Bact.* **53**:255-262, 1941.
6. *Idem.* Changes in adhesiveness of blood platelets, following parturition and surgical operations. *J. Path. & Bact.* **54**:461-468, 1942.
7. Newburger, B. Early postoperative walking. II. Collective review. *Surgery* **14**:154-162, 1943.
8. White, P. D. Pulmonary embolism and heart disease: review of twenty years of personal experience. *Am. J. M. Sc.* **200**:577-581, 1940.
9. Welch, C. E., and Faxon, H. H. Thrombophlebitis and pulmonary embolism. *J. A. M. A.* **117**:1502-1508, 1941.
10. Homans, J. Pulmonary embolism due to quiet venous thromboses and simulating cardiac and pulmonary disease. *New Eng. J. Med.* **229**:309-314, 1943.
11. *Idem.* Deep quiet venous thrombosis in lower limb: preferred levels for interruption of veins: iliac sector or ligation. *Surg. Gynec. & Obst.* **79**:70-82, 1944.
12. Ochsner, A., and DeBakey, M. Thrombophlebitis and phlebothrombosis. *South. Surgeon* **8**:269-290, 1939.
13. *Idem.* Intravenous clotting and its sequelae. *Surgery* **14**:679-690, 1943.
14. Welch, C. E., Faxon, H. H., and McGahey, C. E. Application of phlebography to therapy of thrombosis and embolism. *Surgery* **12**: 163-183, 1942.
15. Allen, A. W., Linton, R. R., and Donaldson, G. A. Thrombosis and embolism: review of 202 patients treated by femoral vein interruption. *Ann. Surg.* **118**:728-740, 1943.
16. Fine, J., and Sears, J. B. Prophylaxis of pulmonary embolism by division of femoral vein. *Ann. Surg.* **114**:801-812, 1941.
17. Fine, J., Frank, H. A., and Starr, A. Recent experiences with thrombophlebitis of lower extremity and pulmonary embolism: value of venography as diagnostic aid. *Ann. Surg.* **116**:574-597, 1942.
18. deTakats, G. Postoperative thrombosis and embolism. *Illinois M. J.* **79**:25-32, 1941.
19. McGinn, S., and White, P. D. Acute cor pulmonale resulting from pulmonary embolism. *J. A. M. A.* **104**:1473-1480, 1935.
20. Murnaghan, D., McGinn, S., and White, P. D. Pulmonary embolism with and without acute cor pulmonale, with especial reference to electrocardiogram. *Am. Heart J.* **25**:573-597, 1943.
21. Currens, J. Electrocardiogram in pulmonary embolism. *Proc. Staff Meet., Mayo Clin.* **17**:502-509, 1942.
22. dos Santos, J. C. La phlébographie directe. *J. int. de chirurgie* **3**: 625-669, 1938.
23. Bauer, G. Venographic study of thrombo-embolic problems. *Acta chir. Scandinav.* Supp. **61**, 1940. 75 pp.
24. Starr, A., Frank H. A., and Fine, J. Venographic diagnosis of thrombophlebitis of lower extremities. *J. A. M. A.* **118**:1192-1195, 1942.
25. DeBakey, M. E., Schroeder, G. F., and Ochsner, A. Significance of phlebography in phlebothrombosis. *J. A. M. A.* **123**:738-744, 1943.
26. Murray, G. Heparin in thrombosis and blood vessel surgery. *Surg., Gynec. & Obst.* **72**:340-344, 1941.
27. Evans, J. A. Dicumarol therapy in thrombotic emergencies. *New Eng. J. Med.* **230**:131-135, 1944.
28. Editorial. Prevention of venous thrombosis. *J. A. M. A.* **124**:778, 1944.
29. Rhoads, J. E., Walker, J., and Panzer, L. Control of blood coagulability with coumarin and other drugs: use of basal doses of dicoumarol with intramuscular injections of heparin for sustained anticoagulant effect. *Northwest Med.* **42**:182-185, 1943.
30. Bryson, J. C., and Code, C. F. Prolonged anticoagulant action of heparin in beeswax mixture. *Proc. Staff Meet., Mayo Clin.* **19**: 100-108, 1944.
31. Loewe, L. Rosenblatt, P., and Lederer, M. New method of administering heparin. *Proc. Soc. Exper. Biol. & Med.* **50**:53-55, 1942.
32. Barker, N. W., Allen, E. V., and Waugh, J. M. Use of dicoumarol [3,3'methylenebis (4-hydroxycoumarin)] in prevention of postoperative thrombophlebitis and pulmonary embolism. *Proc. Staff Meet., Mayo Clin.* **18**:102-107, 1943.
33. DeBakey, M. Dicoumarin and prophylactic anticoagulants in intravascular thrombosis. *Surgery* **13**:456-459, 1943.
34. deTakats, G. Heparin tolerance: test of clotting mechanism. *Surg., Gynec. & Obst.* **77**:31-39, 1943.

35. Shackelford, R. T., and Whitehill, R. Successful ligation of left common iliac vein, for thrombophlebitis complicated by pulmonary emboli. *Bull. Johns Hopkins Hosp.* **73**:307-312, 1943.
36. Homans, J. Exploration and division of femoral and iliac veins in treatment of thrombophlebitis of leg. *New Eng. J. Med.* **224**: 179-186, 1941.
37. Collins, C. G., Jones, J. R., and Nelson, E. W. Surgical treatment of pelvic thrombophlebitis: ligation of inferior vena cava and ovarian veins: preliminary report. *New Orleans M. & S. J.* **95**: 324-329, 1943.
38. Cornil, L. Mosinger, P., and Audier, M. Les interrelations artério-veineuses pathologiques des membres: conceptions pathogéniques. *Presse méd.* **45**:409-412, 1937.
39. Veal, J. R. Prevention of pulmonary complications following thigh amputations by high ligation of femoral vein. *J. A. M. A.* **121**: 240-244, 1943.
40. Atlas, L. N. Ligation of inferior vena cava — case report. *Ohio State M. J.* **39**:917, 1943.
41. Linton, R. R., Morrison, P. J., Ulfelder, H., and Libby, A. L. Therapeutic venous occlusion: its effect on arterial inflow to extremity, as measured by means of Rein thermostromuhr. *Am. Heart. J.* **21**:721-742, 1941.
42. Friedland, C. K., Hunt, J. S., and Wilkins, R. W. Effects of changes in venous pressure upon blood flow in limbs. *Am. Heart J.* **25**: 631-647, 1943.
43. Bucy, P. C., and Lesemann, F. J. Idiopathic recurrent thrombophlebitis: with cerebral venous thromboses and acute subdural hematoma. *J. A. M. A.* **119**:402-405, 1942.
44. Luke, J. C. Mesenteric venous thrombosis: treatment with heparin. *Lancet* **1**:552, 1943.
45. Schall, L. A. Treatment of septic thrombophlebitis of cavernous sinus. *J. A. M. A.* **117**:581-584, 1941.
46. Lyons, C. Treatment of staphylococcal cavernous sinus thrombophlebitis with heparin and chemotherapy. *Ann. Surg.* **113**:113-117, 1941.
47. Adams, J. C. Etiological factors in varicose veins of lower extremities. *Surg., Gynec. & Obst.* **69**:717-725, 1939.
48. Veal, J. R., and Hussey, H. H. Pathologic physiology of circulation in acute thrombophlebitis and post-thrombotic syndrome. *Am. Heart J.* **23**:390-409, 1942.
49. Eger, S. A., and Casper, S. L. Etiology of varicose veins from anatomic aspect, based on dissection of 38 adult cadavers. *J. A. M. A.* **123**:148, 1943.
50. Krumbhaar, E. B., and Ehrich, W. E. Frequent obstructive anomaly of mouth of left common iliac vein. *Tr. A. Am. Physicians* **57**: 196-198, 1942.
51. Chapman, E. M., and Asmussen, E. On occurrence of dyspnea, dizziness and precordial distress occasioned by pooling of blood in varicose veins. *J. Clin. Investigation* **21**:393-399, 1942.
52. Mayerson, H. S., Long, C. H., and Giles, E. J. Venous pressures in patients with varicose veins. *Surgery* **14**:519-525, 1943.
53. Atlas, L. N. Hazards connected with treatment of varicose veins. *Surg., Gynec. & Obst.* **77**:136-140, 1943.
54. Pratt, G. H. Results of surgical treatment of varicose veins. *J. A. M. A.* **122**:797-800, 1943.
55. Bellis, C. J., and Churney, O. L. Injection of varicose veins: importance and technique of injecting elevated extremity. *Surgery* **13**:411-415, 1943.
56. Pearce, M. B. Varicose veins: new technique resulting in rapid obliteration of venous channels without formation of usual large thrombi. *Surgery* **14**:901-914, 1943.
57. Larson, R. A., and Smith, F. L. Varicose veins: evaluation of observations in 491 cases. *Proc. Staff Meet., Mayo Clin.* **18**:400-403, 1943.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30281

PRESENTATION OF CASE

A seventy-five-year-old housewife entered the hospital because of abdominal pain.

The patient had been in apparent good health until three or four months before admission, when she had the "grippe" for several days. Following this she felt poorly. During the week before entry she had extreme constipation, relieved by high colonic irrigations, and accompanied by considerable anorexia and frequent vomiting. On the evening of admission she suddenly had severe epigastric pain, went into collapse and sweated profusely. She was seen half an hour later. She had severe epigastric pain, which did not radiate, associated with considerable retching and vomiting. The vomitus consisted of clear frothy material. The neck veins were distended, but the venous pressure as measured by raising the arm above the level of the heart was not elevated. The pulse was rapid and weak. The blood pressure, which on one occasion had been recorded as 180 systolic, was found to be 130 systolic, 70 diastolic. After about one hour the pain subsided and she was sent to the hospital.

*On leave of absence.

The patient had had Paget's disease of the bone for many years, without any skull enlargement. For several years she had had one good meal daily but the diet had not been well balanced. Five years before entry she apparently had a similar episode of epigastric pain, which was treated by her physician.

Physical examination on admission showed a poorly nourished, pale, dehydrated woman. The lungs were clear. The heart was enlarged to the left, and the sounds were forceful and regular. There was tenderness in the right upper quadrant and in the epigastrium. The liver edge was palpable.

The blood pressure was 110 systolic, 70 diastolic. The temperature was 97.6°F., the pulse 110, and the respirations 25.

Examination of the blood showed a white-cell count of 21,800, with 87 per cent neutrophils. The red-cell count was 3,430,000, with 9.5 gm. of hemoglobin. The urine had a specific gravity of 1.024 and gave a ++ test for albumin; the sediment contained 6 red cells and 12 white cells per high-power field and occasional coarse granular casts.

Plain films of the abdomen showed all the bones to be markedly decalcified, with coarse trabeculations. Along the brim of the left side of the pelvis there was cortical thickening suggestive of Paget's disease. The kidneys and psoas contours appeared normal. There were no dilated loops of intestine.

X-ray films of the chest showed the lung fields to be radiant. The chest was deep. The pulmonary markings were somewhat prominent. The diaphragm was somewhat depressed. The heart was enlarged in all diameters. The aorta was moderately tortuous.

The evening of admission the patient had a second attack of pain. This time the pain was in the right upper quadrant and radiated to the right shoulder. She became cold and clammy, with a rapid and weak pulse. The blood pressure remained unchanged. The pain was relieved by 1/6 gr. of

morphine. During the night she had two more similar attacks. In the morning she continued to have tenderness in the epigastrium. The neck in the thyroid region seemed swollen. She spoke as if she had a "hot potato in her mouth," and she stated that her throat felt sore. An ice collar applied to the neck and hot gargles seemed to bring about some regression of symptoms.

Twenty-four hours and thirty-six hours after admission the patient had two other attacks of pain in the right upper quadrant radiating to the shoulder. Examination was essentially as before, with the addition of some stridor, which was relieved when she was propped. The pain was relieved by morphine. She was given intravenous fluids and 500 cc. of blood. There was some difficulty in getting into the veins because they were collapsed. On the second hospital day, about forty-eight hours after the onset of her illness, she seemed better and more cheerful but suddenly went into collapse and died.

Differential Diagnosis

Dr. Arthur W. Allen: Let us look at the x-ray films.

Dr. George W. Holmes: The bones show the characteristic decalcification found in aged people. There is nothing in these films to suggest Paget's disease, and that diagnosis must have been made on the basis of other films. There is marked increase in the anteroposterior diameter of the chest, which one often sees in cases of emphysema, and in the other view of the chest the lungs are moderately bright and not inconsistent with this finding. The impression one gets from reading the report is different from that gained from these films. The heart is enlarged, but not strikingly so. There is a good deal of calcification in the bronchial tree and along the line you see here, which is rather confusing. The supracardiac shadow is wide. It does not give the impression of any great degree of tortuosity. There is a shadow above the aorta that could be the root of the innominate artery. Dilatation of the root of the innominate does occur when there are lesions of the aorta itself. In this lateral view the outline of the aorta is not sufficiently clear for me to decide whether it is abnormal. I am surprised that it does not show better. With a normal aorta in a patient of this age, one would expect to see its outline better than one does in this film.

Dr. Allen: There are a number of things about this record that I question, and it would be helpful to have considerable additional information.

Obviously this case must have been considered as a questionable acute abdominal emergency, although there is no note to that effect. The first thing that interests me is that until the patient had what was diagnosed as "grippe" she had been well, and after that she had not been well for a period of three or four months. I do not know what kind of illness this was. The term "grippe" covers a multitude of disorders. It does not say whether she had gastrointestinal symptoms at that time, although people occasionally classify some types of gastroenteritis under the general heading of grippe. The record does not state whether the patient had any fever through the months before her acute illness. It is possible that she had a low-grade fever with her prolonged malaise.

The week prior to entry she had extreme constipation, which is not unusual in a woman of seventy-five who is as thin as the x-ray films show this patient was. These elderly people frequently have obstipation. We are told that the constipation was relieved by high colonic irrigations, so it appears that this episode five days prior to entry was not due to intestinal obstruction. The severe sudden pain probably was not associated with the colonic irrigation. I assume that it was not because I think that it would have been so stated if there had been any relation. Of course, sudden severe abdominal pain from perforation of a diverticulum or from perforation of a weak spot in the bowel sometimes does follow irrigation of the colon. The pain was sudden and severe and in the epigastrium. She went into collapse and sweated profusely, and her physician apparently saw her within half an hour. He obviously was impressed with the fact that she was quite ill, because as soon as he could arrange it, she was brought to the hospital. They state that the epigastric pain did not radiate, and that may have been true. It is possible that she was in considerable shock either from pain or from the trouble that had brought on the pain; if so, she might not have been able to differentiate too well whether the pain started in the epigastrium or to where it radiated. She did have retching and vomiting, however, which probably arose not from the pain or from the morphine but from the lesion itself.

The statements that the neck veins were dilated and, later, that there was swelling in the thyroid region bother me a great deal and I have difficulty tying those together with the rest of the picture. They may be important in the differential diagnosis, but I am unable to link them up with the lesion that I believe this woman had.

She had a drop in blood pressure, which indicates shock, and farther on we see that the red-cell count was 3,500,000, with 9.5 gm. of hemoglobin, indicating the possibility of blood loss. Later in the record we see that she had been having one meal a day, and it is stated definitely that the diet was deficient; so possibly, and quite probably, the red-cell count and hemoglobin were about as reported, even before the episode of acute illness came on. One of the important pieces of data that we are given is the leukocytosis of 21,800, with a differential count of 87 per cent neutrophils. It is unusual to get that amount of leukocytosis with an elevation of the neutrophils on the basis of anything else except inflammation or gangrene. To be sure, it does occur with rupture of the spleen; but this

woman had had no injury, and we have no reason to suppose that that was what she had. Bleeding into the peritoneal cavity from a ruptured aneurysm or ectopic pregnancy will cause some elevation in the leukocytes, but not to this degree. Mesenteric thrombosis produces extreme leukocytosis, but Dr. Wyman Richardson has recently told us that an elevated leukocyte count in mesenteric thrombosis is not often associated with an increase in the ratio of the polymorphonuclear cells. None of the surgical service were aware of this, and the one patient on whom we have had an opportunity to test this point since we received the information was apparently an exception to the rule because she had the same elevation of neutrophils that the patient described here had.

Could the "grippe" have actually been an endocarditis? Did she go on for a period of three or four months and then develop thrombi that were given off and finally went into the arterial circulation of the mesentery? This would explain the entire picture in spite of the fact that we have no evidence of a distended bowel in the flat film of the abdomen. One early x-ray examination may be of no particular value. We have little in the record telling us about the final examination so far as the abdomen is concerned. The suddenness of the onset, the severity of the pain, the associated vomiting, which was nonfecal, and the high leukocyte count, — in mesenteric thrombosis it may be much higher than it was in this patient, — all occurring three months after some kind of illness, may form the basis on which to reconstruct this case. The difficulty is that she lived a little long for mesenteric thrombosis of the usual progressive type. Also, it states that on the second hospital day, forty-eight hours after the onset of the illness, she seemed more cheerful but suddenly collapsed and died, which suggests further progression, either perforation of a hollow viscus or something that had to do with the cardiovascular system.

I shall leave the discussion at this point and say that this patient had arteriosclerotic disease and Paget's disease, with all due respect to Dr. Holmes. Also, there was an acute affair, which, I believe, is more likely to have been mesenteric thrombosis than anything else. Of course one must consider the possibility of other acute diseases that involve the upper abdomen, such as perforated ulcer, which would be all right for the length of time she lived, or acute cholecystitis. Patients do not die suddenly from acute cholecystitis; but, when they do, it is usually within a few minutes after the gall bladder ruptures.

DR. CHESTER M. JONES: This patient's symptoms were interesting in that they were referable to the throat and that she had swelling there. Can you tie those facts in with the symptoms of the abdomen? It seems to me that she died of symptoms referable to the neck.

DR. ALLEN: They say that there was definite improvement following the application of an ice collar. I cannot tie the neck symptoms with those of the abdomen. Have you any idea?

DR. JONES: No, except that she had swollen neck veins, which suggest something vascular.

DR. J. H. MEANS: The neck bothered me a good deal. I could not laugh it off, nor could I hook it up with the abdominal diagnosis unless it was on a vascular basis. The story of sudden onset, of doing better and suddenly dropping dead makes one wonder if she had a cerebral embolus. Dr. Allen has suggested the possibility of endocarditis, which is a good one. If she had had one embolus going to the mesentery, she could also have had one going to the cerebrum and causing sudden death. The findings in the neck associated with sudden death remind me of a case that I discussed in which there was sudden demise during a thyroid operation, which turned out to have been due to a cerebral embolus. It seems to me that it is easy to hook up the various phenomena present here on the basis of some kind of cardiovascular or vascular lesion, but precisely what, is difficult to say. Knowing the department's diabolical ingenuity in framing us, and since the first case discussed today was a dissecting aneurysm, I wonder if they might have lined up two dissecting aneurysms for us. It is conceivable, although I am throwing the suggestion out very cautiously.

DR. JACOB LERMAN: When I first saw the patient it was quite obvious that she was in shock. She was exquisitely tender over the epigastrium and had recurring attacks of pain, which finally shifted to the right side. My attention focused on the gall bladder. Consequently I had a surgeon see her, who agreed it was probably an episode of acute cholecystitis. He did not advise surgery, however, because her condition was so poor. She had an anemia, which was greater than that indicated by the red-cell count of 3,500,000, because she was dehydrated when the count was taken. I also was disturbed by the distended veins and by the swelling of the neck, which was definite and did not recede until an ice collar was applied. I raised the question of acute thyroiditis. It was difficult to explain the swelling of the neck and the stridor. The latter improved on elevation of the head. We thought that these symptoms were secondary to throat infection, and let it go at that.

CLINICAL DIAGNOSES

Acute cholecystitis, with perforation?
Paget's disease.

DR. ALLEN'S DIAGNOSES

Mesenteric thrombosis (secondary to subacute bacterial endocarditis).
Arteriosclerotic disease.
Paget's disease.

Anatomical Diagnosis

Aortic aneurysm (? syphilitic), with rupture into mediastinum and right pleural cavity and hemorrhage into soft tissues of neck and walls of esophagus and stomach.

Pathological Discussion

Dr. Benjamin Castleman: The autopsy on this patient showed an extremely interesting lesion. When we opened the abdomen, the first thing that struck us was the marked hemorrhagic appearance of the surface of the stomach. There was no free blood in the abdominal cavity; the blood appeared to be in the wall of the stomach, extending down from the cardia to about the beginning of the antrum. When the chest plate was removed, about a liter of fresh blood was found in the right pleural cavity, and this hemothorax was undoubtedly the cause of the sudden exitus. The source of this hemorrhage was a perforation of an aneurysm of the descending thoracic aorta. The entire mediastinum was filled with blood clot, some obviously very recent from the terminal rupture and some definitely older. It was this older blood that had apparently been oozing from a subacute perforation of the aneurysm and had extended up into the neck. We found a huge amount of blood surrounding all the vessels of the neck and compressing the esophagus. The blood had permeated through the outer coat of the esophagus and had extended as a hematoma between the muscle layers and the adventitia. When it reached the stomach, a large part of the blood entered the muscle layers of the stomach and appeared as a submucosal hematoma, which bulged into the lumen. The appearance was not unlike that seen in intramural tumors of the stomach, such as leiomyomas and neurofibromas. The aneurysm was saccular, measured 6 cm. in diameter and was probably syphilitic in origin. There was no dissection of the aorta.

In retrospect, the peculiar appearance of the aorta in the x-ray film that Dr. Holmes mentioned was of some significance.

Dr. Holmes: The x-ray appearance may be explained on the basis of the pathology demonstrated. The enlarged root of the aorta and the absence of the shadow of the descending aorta in the lateral view were in all probability due to the blood surrounding these vessels.

CASE 30282

Presentation of Case

A twenty-five-year-old woman was admitted to the hospital because of bleeding from the nose and the gums.

The patient had apparently been well until the age of seventeen, when she developed recurrent attacks of sneezing and shortness of breath over a period of one year. She experienced considerable fatigue and lost about 30 pounds in weight. She was admitted to a community hospital, where diagnoses of bronchial asthma, chronic sinusitis and bronchitis were made, and she was treated with ephedrine and potassium iodide. Many skin tests were positive and she was advised to regulate her habits accordingly. She was discharged but reentered that hospital five months later because of nausea and vomiting of two weeks' duration. The blood pressure was 150 systolic, 105 diastolic. The white-cell count ranged between 10,000 and 20,000, with an eosinophilia of 6 to 30 per cent. While in the hospital she developed anemia. The urine showed albumin, red cells, white cells and hyaline and granular casts. One serum protein determination was reported as 9.1 gm. per 100 cc. A diagnosis of periarteritis nodosa was entertained, but a muscle biopsy was negative. The symptoms apparently cleared up; she was discharged after two months in the hospital and remained symptom free for about a year. At the end of that period, following an upper respiratory infection, she had recurrence of the asthma and re-entered the same hospital. Examination showed expiratory and inspiratory wheezes and groans, but no rales or dullness. The blood pressure was 160 systolic, 125 diastolic. The urine concentrated as high as 1.032 and showed a variable amount of albumin. The sediment almost constantly revealed 1 to 2 red cells, 2 white cells and 5 to 20 coarsely granular and hyaline casts per high-power field. The total urine albumin output varied from 2.6 to 18 gm. Phenolsulfonephthalein excretion tests were all in the neighborhood of 25 per cent of the dye in two hours. Both kidneys showed equally poor function, but cultures were negative. The blood nonprotein nitrogen varied from 49 to 26 mg. per 100 cc., and the total protein was 7 gm., with an albumin of 3 to 4.7 gm. and a globulin of 2.7 to 3.4 gm. The blood calcium was 12 mg. per 100 cc., and the blood phosphatase 4.4 mg. The asthma was rapidly brought under control. She was asymptomatic, but displayed little if any improvement in the kidney function and was finally discharged on the fifty-seventh hospital day. Following discharge she felt well until one and a half months before admission to this hospital, when she contracted an upper respiratory infection. Her nose started to bleed; at first the bleeding was spotty, but then it gradually increased. The bleeding occurred without any apparent exciting cause every two or three days and lasted for two or three hours. One month before entry bleeding from the gums was noted which was most marked from the region of the molars and alternated from one side of the mouth to the other. This continued for five or six hours at a time and was occasionally temporarily alleviated by the application of Dermital lotion and alum. The bleeding was more apt to occur at night, when she would wake up with a

mouthful of blood. During this period she noticed an itching sensation in the eyes, black and blue spots on the legs and, for two weeks before entry, swelling of the ankles, which disappeared with bed rest. She missed one menstrual period at the onset of this illness, and the second one, which started eight days before entry, was associated with much pain and many large clots, neither of which was normal. She had had some morning nausea without vomiting, but denied any possibility of pregnancy. Her physician had given her calcium gluconate without any effect.

During this six-year period she had had no fever except that associated with upper respiratory infections; she had also had no chills, joint pains, dysuria, hematuria, pyuria, incontinence or increased frequency. She had had measles, diphtheria, bronchitis and influenza as a child. Following diphtheria, at the age of fourteen, she had "kidney trouble," which kept her in bed for many months.

Physical examination showed a well-developed, moderately undernourished pale woman in no distress. A small amount of blood oozed from the nose. Some coagulated blood was present on the gums. A few squeaks were heard over the lung fields. The left border of cardiac dullness was 11 cm. to the left of the midline in the fifth space. The first sound was loud, and there was a grating early apical systolic murmur. The abdomen was negative. Numerous black and blue areas were present on both thighs. No skin nodules were palpable.

The blood pressure was 172 systolic, 98 diastolic. The temperature was 99°F., the pulse 112, and the respirations 22.

Examination of the blood showed a red-cell count of 1,420,000, with 50 per cent hemoglobin. The white-cell count was 6300, with 58 per cent neutrophils, 17 per cent lymphocytes, 6 per cent monocytes and 12 per cent eosinophils. During her entire stay, except as noted, the urine had a reaction of pH 6.0 and a specific gravity of 1.010. It showed a +++ test for albumin, and the sediment contained occasional white and red cells. A blood Hinton test was negative. The blood nonprotein nitrogen was 129 mg. per 100 cc., and the protein 6 gm. The prothrombin time was 21 seconds (normal, 18 seconds).

She was given blood transfusions. Various measures to control the bleeding were at first unsuccessful. She was placed on a high-vitamin and high-calorie diet. On the fourth hospital day the blood chloride was 117 milliequiv. per liter, and the sodium 146.8 milliequiv. The blood calcium was 9 mg., and the phosphorus 3.1 mg. per 100 cc.; the carbon dioxide combining power was 9.9 millimol. per liter. An x-ray examination of the chest showed rather diminished linear shadows behind the heart and the left hilus. The heart size was within normal limits. The aorta was more tortuous than usual.

On the seventh hospital day a gallop rhythm was heard. In addition, one or two observers heard a mid-diastolic rumble. An electrocardiogram showed a normal rhythm of 90. The PR interval was 0.20 second, and T_1, T_2 and T_3 were upright. QRS demonstrated slight tendency to low voltage. The axis was normal. The patient was placed on a daily regime of 3 gr. of digitalis, a fluid intake of 1700 to 2500 cc., 0.8 to 1 gm. of protein per kilogram of body weight, 7 to 10 gm. of sodium chloride, and 3 to 6 gm. of sodium bicarbonate.

On the thirteenth hospital day intermittent bleeding from the gums was noted, which was temporarily controlled by adrenalin packs, fibrin foam and raw beef and she was transfused with blood. The urinary output was 1000 cc. on an intake of 200 cc. The pH of urine was 6.5, and it gave a ++++ test for albumin. A blood nonprotein nitrogen was reported as 35 mg. per 100 cc., the chloride 107.1 milliequiv. per liter, and the carbon dioxide combining power 15.7 millimol. per liter. The sodium was 141.8 milliequiv. per liter, and the calcium 8.8 mg. per 100 cc. On the fifteenth hospital day the patient had considerable gastric discomfort, which was relieved after digitalis was stopped. In the course of the next few days she experienced headaches, dizziness, and pain and light flashes in the eyes. Fundal examination showed spasticity and narrowing of the arterioles without any exudate. A blood nonprotein nitrogen five days after the preceding determination was 34 mg. per 100 cc., and the carbon dioxide combining power 23 milliequiv. per liter. These two low nonprotein nitrogen determinations occasioned much confusion and mystification and premature rejoicing at the wonders of modern therapy until a repeat nonprotein nitrogen, six days later, was found to be 129 mg. per 100 cc. Because of the persistence of the intermittent bleeding from the gums, which was sometimes fairly profuse, various dental measures, such as extraction of certain of the teeth and correction of faulty occlusion, were contemplated but deemed inadvisable. On the thirtieth hospital day, the nonprotein nitrogen was 164 mg. per 100 cc., the chloride 96 milliequiv. per liter, and the carbon dioxide combining power 16 millimol. per liter. A blood urea nitrogen was 142 mg. per 100 cc. Two urea-clearance tests were 41 and 54 per cent normal. A phenolsulfonephthalein test showed no excretion in two hours. The urinary output was between 250 and 750 cc. daily on an intake of 1500 to 2000 cc. The pH of urine was 7.0 to 7.5, but the urinalysis was the same as before.

On the forty-second hospital day she developed anorexia, nausea, vomiting, increasing headache and dizziness, weakness, and bleeding from the gums and nose. She started to wheeze, ankle edema appeared, and there were transient episodes of numbness of the legs. A precordial friction rub was heard. The abdomen became distended. The urinary out-

put was below 250 cc. on an intake of 1500 cc. The nonprotein nitrogen was 186 mg. per 100 cc., the chloride 96 milliequiv. per liter, and the red-cell count 1,660,000. The nonprotein nitrogen gradually rose to 250 mg. per 100 cc., the chloride fell to 83 milliequiv. per liter, the blood protein remained over 6 gm. per 100 cc., and the calcium was 6.6 mg.

On the fifty-fourth hospital day the patient had a scattered papulopurpuric eruption on the face and trunk and considerable itching. Nausea and vomiting of dark-brown material continued, and she developed diarrhea; the precordial friction rub became extremely loud. She died on the fifty-ninth hospital day.

Differential Diagnosis

Dr. Austin Brues: This seems clearly to be a case of progressive renal failure terminating in uremia, with classic signs and symptoms. The somewhat temperamental nonprotein nitrogen level seems unnecessary for making a diagnosis of terminal uremia in view of a number of other observations, namely, hypertension, hemorrhagic diathesis, friction rub, anorexia, vomiting and diarrhea. We may therefore check off those findings in the case that are characteristic of renal failure and proceed to consider its etiology.

The question to be answered is, Was this a primary or localized disease of the kidney, or was it part of a more generalized disease, as was suggested in the hospital to which the patient was admitted some years ago?

On reading over the case the course of the disease appears to be that of a chronic glomerulonephritis following acute glomerulonephritis, with an acute exacerbation in the interval that has been described in detail. The first suggestion in the history that the patient had kidney disease occurs when she was said to have been confined to bed following diphtheria. It is worth pointing out that the type of acute kidney disease that progresses to chronic nephritis is rare following diphtheria and is frequent following streptococcal infection. We must consider that she possibly had a streptococcal infection along with the diphtheria or that in reality she had a streptococcal infection, if we are to take this seriously as part of the history. This was followed by a course which, so far as we are able to tell from the history, was characterized at times by a moderately elevated blood pressure, with a high diastolic pressure. Later, there was evidence of cardiac hypertrophy, clinically but not by x-ray examination, and evidence of change in the aorta beyond what is normal for her age.

The urinary findings showed albuminuria and red and white cells and casts in the sediment, the cells having been at all times apparently moderate in number. She showed a progressive anemia toward the end of her course. There appears to be a plethora of laboratory findings, some of which are difficult to interpret. In particular, I should say that the terminal observation that the urea clearance was half of normal, whereas the patient failed to excrete phenol red during the course of the two hours, appears paradoxical. It seems clear that the patient had acidosis at her final admission, and the therapy for this acidosis was fairly successful. It also appears that some cardiac failure was present terminally, although the x-ray studies failed to show enlargement.

Regarding the probable anatomic findings, the presence of considerable albuminuria in the last stage of this condition suggests that the patient had not reached the stage of the very contracted kidneys of an extreme terminal, chronic glomerulonephritis.

With regard to the differential diagnosis of disease localized in the kidney, there seems to be little in this case to suggest another diagnosis. The absence of fever and chills and the extremely long course are against focal embolic nephritis from endocarditis, although cardiac murmurs were noted and they may have changed in the course of observation. There is no good evidence for pyelonephritis, and at one time a culture of the urine was made and found to be negative. Polycystic kidneys would hardly occur without a palpable mass on at least one side. I think that similarly obvious considerations are against renal tuberculosis and amyloidosis.

Regarding general diseases in which the renal phenomena may be prominent, although the patient had eosinophilia, anemia and a bleeding tendency, there is no special reason to assume the presence of leukemia, Hodgkin's disease or some other tumor that happened to involve both kidneys and the bone marrow.

I should like to consider why periarteritis nodosa was entertained as a possible diagnosis on the previous admission. Presumably this was because, in addition to the nephritis and hypertension, the patient had a high total protein and eosinophilia. Some consideration might also have been given to the pulmonary symptoms, suggesting that she had arterial disease involving the lung. There is, however, no evidence of a positive sort for this diagnosis, attractive as the thought might have been that such a diagnosis could be made during life. The fact that the patient apparently recovered during the interval between the previous admission and the present one is not necessarily against the diagnosis of periarteritis nodosa, because periarteritis nodosa does undergo remissions. Is there any possibility that the patient had periarteritis nodosa on the basis of sensitivity to sulfonamide drugs? All it is possible to say is that we have no evidence that the patient was subjected to sulfonamide therapy, although she had had a great many infections, particularly upper respiratory infections. It is entirely possible that such therapy may have

been given from time to time and forgotten. On the other hand the previous trouble occurred several years previously, possibly before sulfonamides were in common use. I therefore think that the diagnosis of periarteritis nodosa or other generalized vascular disease ought to be considered improbable, and that it is reasonable to make a diagnosis of chronic glomerulonephritis. If there is a radiologist here, I should like to have him comment on the diminished linear shadows in the chest.

DR. JOSEPH B. AUB: Is the lateral spine normal? Are the vertebras normal?

DR. BENJAMIN CASTLEMAN: There is no radiologist here.

DR. WYMAN RICHARDSON: This patient was on the service for almost two months when I was visiting. We reached the same conclusion that Dr. Brues has, namely, that she had chronic glomerulonephritis. We simply toyed with the idea of periarteritis nodosa. She had an enlarged heart, and I do not know why it does not show by x-ray. She had a definite gallop rhythm, and we had the usual futile discussion concerning mid-diastolic murmurs. I was very much on the fence in this matter of murmurs, and I am quite ashamed of my note in the record. The thing that troubled the girl the most was the bleeding, and it also troubled me a great deal to explain it, although it is frequent with renal failure. It is suggested that the bleeding is due to toxic damage, whatever that may mean.

DR. BRUES: I see no mention of platelets.

DR. RICHARDSON: They were numerous.

I found it difficult not to take a completely defeatist attitude in regard to therapy and decided to send the girl home when the bleeding seemed to stop somewhat. The service felt that we ought to try to correct the chemical situation, which I think was the proper attitude to take. In spite of the fact that the acidosis was considerably improved, I could not see that the patient herself was any better. She went downhill from that point on.

DR. ALLAN M. BUTLER: I was asked to see the patient to render advice whether the bleeding was due to vitamin C deficiency. It was my opinion that a plasma ascorbic acid determination was not worth doing because it would give relatively little information in appraising vitamin C deficiency. For even if the plasma vitamin C were zero, it would not mean that the bleeding was due to a vitamin C deficiency. If, however, the white-cell and platelet content of ascorbic acid were reduced it would mean that the patient was suffering a deficiency severe enough to cause this hemorrhagic tendency. At that time, however, the laboratory was too busy with war work to determine the vitamin C content of the white cells and platelets. I suggested a therapeutic trial of vitamin C. Since the diet did not suggest deficiency, I thought that the bleeding was associated with the hypertension and anemia. I recommended transfusing the patient before resorting to digitalization, and before seeing if magnesium sulfate would affect the hypertension. It also seemed to me that an appraisal ought to be made of the renal function before any consideration was given to the desirability of doing a sympathectomy. As intravenous pyelograms had been taken at the other hospital, I suggested that it would be wise to get hold of them to see if any information could be obtained about possible anatomical anomalies that might be behind the renal disease.

The odd nonprotein nitrogen values are a good example of doing quantitative chemistry with technicians who are not expert chemists. The reason these two falsely low determinations were obtained is that the technician who did them carelessly added too much acid so that the final reaction was not alkaline enough and the color did not develop. It is the kind of error that crops in if technicians are not properly trained in the methods of quantitative chemistry.

The final thing is that the lack of blood pressures in the history as recorded here makes it hard to decide what went on in this patient. One wonders how much of the primary difficulty was cardiac failure and how much was due to renal failure.

DR. CASTLEMAN: Two days before she died the blood pressure was 115 systolic, 70 diastolic; the day before she died it was 130 systolic, 75 diastolic.

DR. BUTLER: She was obviously having considerable cardiac failure.

DR. RICHARDSON: She had pericarditis and a friction rub, and probably had ulcers of the bowel. I should like to take exception to something Dr. Butler said. I do not see why the bleeding was due to anemia and high blood pressure. High blood pressure may cause rupture of an artery, but not oozing from the gums and capillary bleeding. Nor does anemia cause it, unless there is a lack of platelets, or except in certain cases of myelogenous leukemia.

DR. BUTLER: You know more about that than I. In my limited clinical experience, purpura in the presence of severe anemia is not uncommon.

DR. AUB: Uremic patients bleed without vitamin C deficiency. One can "pass the buck" by saying it is due to anemia, but they bleed no matter how one explains it.

DR. BUTLER: Rheumatic fever patients may have considerable purpura.

DR. RICHARDSON: That is probably capillary; this is probably capillary bleeding too. I think it is fair to assume that it was due to toxic effect on the capillaries, but after all, this statement does not mean anything.

DR. BUTLER: It is interesting, also, that when I saw this patient, ten days after admission, she did not have any retinitis in spite of the long-standing hypertension. She had constriction of the retinal arteries and thickening of the brachial and radial arteries but no real retinitis.

Clinical Diagnosis

Chronic glomerulonephritis.

Dr. Brues's Diagnosis

Chronic glomerulonephritis.

Anatomical Diagnoses

Chronic glomerulonephritis.
(Uremia.)
Cardiac hypertrophy, hypertensive type.
Septicemia (*Staphylococcus aureus*).
Endocarditis, chronic rheumatic: mitral valve.
Parathyroid hyperplasia, secondary.
Renal osteitis fibrosa.
Hemorrhages into skin, pleura, lungs, pericardium, gall bladder, esophagus and ileum.
Acute esophagitis, terminal, uremic.
Acute ileitis, terminal, uremic.

Pathological Discussion

Dr. Castleman: The autopsy on this woman showed a pair of kidneys that weighed 90 gm., one weighing 40 gm., and the other 50 gm.; they had the typical appearance of chronic glomerulonephritis. The surfaces were uniformly coarsely granular, and the cortices were narrow, measuring 2 to 3 mm. Microscopic examination confirmed that diagnosis. Practically every glomerulus was diseased; most of them were completely wiped out and hyalinized, and others showed characteristic crescents and capsular adhesions. There were foci of tubular dilatation and of atrophy. All parathyroid glands were quite large, weighing together 0.5 gm., which is three or four times the normal weight, and which indicates that the renal insufficiency had been going on for a long time. Further corroboration of that was the fact that the bones showed early osteitis fibrosa. Quite possibly the vertebras were a little osteoporotic, Dr. Aub, because the intervertebral disks, as you can see from this roentgenogram, are ballooned out, suggesting that the bones themselves were soft. Some marrow spaces were completely replaced by connective tissue, which was also present along some of the bone trabeculae. This is a mild form of the lesions one sees in a child with renal rickets.

There were numerous hemorrhages throughout the body, including the lungs. If these pulmonary hemorrhages became confluent, I wonder if they might produce the picture in x-ray films that the radiologist calls edema associated with nephritis.* There were recent ulcers, probably on a uremic basis, of the small intestine, not of the colon, which is more frequently involved in uremia, and also ulcers in the esophagus. The heart was enlarged, weighing 350 gm., and the left wall was hypertrophied. The murmur was due to a slight but definite degree of stenosis of the mitral valve on a rheumatic basis; but there was no evidence of acute rheumatic infection.

*Scott, T., Schatzki, R., and Bauer, W. Pulmonary edema: its roentgenologic appearance in acute glomerulonephritis without signs of cardiac failure. *J. A. M. A.* **114**:613, 1940.

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TRANSFUSION WITH BLOOD AND ITS DERIVATIVES AND SUBSTITUTES

The stimulus of war has brought rapid advances in the practical application of certain fields of medical knowledge. In no field is this more marked than in the field of transfusion. The tremendous feat of wholesale blood collection, which has been carried on throughout the country by the Blood-Donor Service of the American Red Cross, has conditioned the American people to the donation of their blood and has started, it is to be hoped, a movement that will not cease when the war ends. From the blood that has been collected, a large amount of dried plasma has been made available for shipment all over the world to the armed forces. Every American on the streets today knows that this has contributed materially to the reduction in mortality from wounds on all the fighting fronts. Recent reports indicate that the red cells, previously wasted, may be resuspended, and distributed to civilian hospitals for administration to anemic patients.

Another development from the Red Cross program has been the large-scale fractionation of human plasma into its component parts by methods developed by Cohn and his associates in the Department of Physical Chemistry at the Harvard Medical School. This work was originally started to provide the armed forces with a compact, concentrated blood derivative for emergency use, particularly by highly mobile military troops for whom transportation space is at a premium. Albumin provides the osmotically active fraction of plasma in a very concentrated form, which can be injected rapidly and safely without reactions, and with a rapid increase in blood volume resulting from the drawing of water from the tissue spaces into the blood stream. The possible uses of such an osmotically active and safe concentrated solution in clinical medicine and surgery are manifold.

The fractionation program provides not only albumin for the treatment of shock and conditions associated with hypoproteinemia but also other globulin constituents of the plasma that have important functions. Two of these products have already found useful applications in the clinic. Fibrin foam, which is derived from the clotting elements of the blood, has been shown to have remarkable hemostatic properties for use in neurosurgical operations. The gamma globulin of human serum has been used successfully for the prevention or modification of measles, its advantages being its availability, reproducibility, potency and freedom from substances producing reactions. Further developments of this program should provide the clinician with many new and useful tools — safe because they are derived from human sources — that can be applied to the treatment of disturbances of normal physiology.

The statement by the Subcommittee on Blood Substitutes of the National Research Council, which appears elsewhere in this issue of the *Journal*, indicates that the same type of careful study has been applied to blood *substitutes* that have been suggested for clinical use. Every physician would do well to read this statement, since it indicates the degree to which good clinical practice is dependent on the basic sciences. Here he will find a clearcut statement of why, from a physicochemical point of view, gelatin cannot be considered to be a satisfactory substitute for either blood plasma or albumin, although it may have some effect in the amelioration of the diminution of blood volume that characterizes surgical shock. The report emphasizes the dependence of the physiologic function of any material on its molecular size and shape. Gelatin molecules range from very long thin ones, giving rise to certain undesirable properties, such as rouleaux formation of the red cells and their rapid sedimentation, to molecules so small that their fairly rapid escape from the circulation makes the effect of gelatin less sustained than that of plasma. Furthermore, it is pointed out that "gelatin solutions probably do not contribute significantly to nutrition," and their influence on "the distribution of plasma proteins between circulating blood and tissues should be further investigated."

Replacement therapy should be directed, whenever possible, to actual replacement of what has been lost. In the case of shock due to hemorrhage, this means whole blood. For reasons of practicability, however, it has been found expedient to supply the armed forces, not with whole blood, but with plasma and albumin, which will sustain the patient until such time as he can receive the needed red cells in the form of a transfusion of whole blood or of resuspended cells. In certain types of shock, plasma alone is lost, and for these, plasma is the ideal replacement fluid.

The products of plasma fractionation are individual proteins used in relatively pure state for the treatment of specific deficiencies. They are blood *derivatives*, not blood substitutes and have important properties of their own. Thus, albumin, because of its high osmotic activity may restore blood volume more rapidly than transfusion of an equivalent amount of plasma. The specific properties of purified proteins deserve further exploration, and these blood derivatives give promise of having widespread use in the clinic.

WARTIME POPULATION TRENDS

The Metropolitan Life Insurance Company, in its April issue of the *Statistical Bulletin*, publishes some interesting comparisons of wartime population trends among various countries. The Axis countries, suffering increasing battle losses, are also less able to replenish their populations at home. On the other hand, the United States and Great Britain have shown marked gains in the natural increase in their populations since war broke out. Germany, home of the "master race" that seems doomed never to achieve its mastery, has become again the land of the deepening shadows.

Germany's natural increase of population, according to this reliable source of information, has been dropping steadily since the war began, with the decline becoming more marked each year that the war continues. Thus the excess of the birth rate over the death rate dropped from 8.1 per 1000 population in 1939 (the best year under the Hitler regime) to 2.9 in 1942, the last year for which official figures are available. The year 1942 had the distinction of revealing the lowest rate of increase in Germany for any year since World War I. It can be assumed that, since 1942, the large-scale bombing of German cities, with evacuation of populations, and the heavier concentrations of men on the fighting fronts have further increased the death rate and decreased the birth rate. The old warning that whom the gods would destroy they first make mad seems to be proving its worth again.

Italy, a member of the Axis until 1943, likewise showed a drop of some 40 per cent in the excess of births over deaths — from 10.1 per 1000 in 1939 to 6.1 in 1942, a decline largely due to a decrease in the birth rate. The other Axis countries have shown similar, though less marked, trends.

Of the occupied countries, a mixed situation seems to have existed. Denmark showed an increase in the

margin of births over deaths through 1942. In the Netherlands, the rate of increase rose after an initial fall. Belgium and France are facing serious depopulation, with death rates exceeding birth rates since 1940.

The crude rate of natural increase in the United States has risen to its highest figure in twenty years, with Canada's growth a close parallel. In England, the excess of births over deaths in 1943 was over 175,000, the highest in fifteen years. Figures are not available for China and Russia, but it may be expected that their usual high fertility will again prevail with their soil freed of invaders and their armies returned to the land.

Regardless of what we may believe regarding the selective limitation of populations for the future, it is obvious that population trends among the United Nations are showing a normally healthy situation as compared with those of Central Europe.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Clinic	Date	Clinic Consultant
Lowell	August 4	Albert H. Brewster
Springfield	August 16	Garry deN. Hough, Jr.
Hyannis*	August 22	Paul L. Norton

*Date changed.

WAR ACTIVITIES

NATIONAL RESEARCH COUNCIL

The following statement was recently released by the Subcommittee on Blood Substitutes of the National Research Council.

On the basis of the extensive earlier literature and the recently accumulated evidence, certain statements can be made concerning gelatin solutions prepared for intravenous use and the chemical, physiologic and clinical properties of such solutions compared with those of plasma.

I. Chemical

(1) Plasma is constituted of molecules whose size is known and is related to plasma function. The plasma proteins may be grouped into a few classes, in each of which the molecules are of uniform size and shape. Gelatin and degraded gelatin solutions submitted for study as transfusion fluids show almost continuous variation in size over a very wide range.

(2) Plasma proteins have diameters close to 36 Angstrom units. Most of the particles of gelatin and degraded gelatin have diameters of about half this value, 18 Angstrom units.

(3) The largest part of the plasma proteins do not deviate greatly from symmetrical shape, though fibrinogen, present to a small extent, has long, rodlike molecules. Gelatin appears to be made up of linear polypeptide chains loosely coiled to give very long molecules.

(4) Degradation of gelatin decreases the number of very long particles, which are responsible for the gelation, much of the viscosity and probably other undesirable effects. Degradation increases the number of very small particles, which are responsible for most of the osmotic pressure, though not for the colloid osmotic pressure since they diffuse rapidly through membranes.

(5) A standard technic of degradation of gelatin yields solutions of about the same average molecular weight and the same size distribution. The degree of degradation is best measured by the number of potential peptide linkages that are broken. This number can be determined from the osmotic pressure, or more easily from the viscosity, since the intrinsic viscosity of these solutions is proportional to the number-average molecular weight.

(6) Plasma proteins do not readily diffuse through membranes employed in measuring colloid osmotic pressure. A large part of the degraded gelatin solutions submitted for study as transfusion fluids are of such small size as to diffuse readily through such membranes.*

II. Physiological and Clinical

(1) *It must be recognized that, when available, whole blood, plasma or human serum albumin are the solutions of choice to be employed in the treatment of hemorrhage or shock.*

(2) It has been demonstrated that when the precautions recommended to the gelatin industry are taken, pyrogen-free solutions of gelatin can be prepared.

(3) Such gelatin solutions have been given to man without late toxic reactions.

(4) A small percentage of patients have been found to have immediate reactions. Local thromboses are common when certain preservatives are employed.

(5) Injection of the gelatin solutions have been made without evidence of sensitization.

(6) Many repeated injections in animals have been given without evidence, histologic or clinical, of toxicity or irreversible accumulation.

(7) The solutions of gelatin studied have a definite effect in augmenting cardiac output and circulating blood volume in dogs submitted to hemorrhage and in patients suffering from shock due to hemorrhage or skeletal trauma. The evidence at present indicates that gelatin solutions may have a beneficial effect in burns. There is thus clinical evidence that these solutions have a definite, though temporary, effect in relieving the state of shock; therefore it is often necessary to take recourse to multiple injections.

(8) The smaller molecules on which the osmotic effects of gelatin solutions depend are rapidly lost from the blood stream, largely through the kidneys. In this respect the effect of gelatin may be contrasted with that of the plasma proteins, which are not normally lost through the kidneys, but when present in excess form reserves in the tissues.

(9) The longer rod-like particles of gelatin persist in the blood stream and are presumably responsible for rouleaux formation, for the increased sedimentation rate of the red cells and for the changes in the distribution of plasma proteins between the blood stream and the tissues.

III. Limitations and Unanswered Questions

(1) *The solutions gel at about 20°C. and therefore cannot be used in cool or temperate climates in the field.*

(2) *Proper typing of blood following the administration of gelatin solutions may be difficult. This problem should be studied further. It may be essential to warn that a sample of blood for typing should be withdrawn from each patient before the administration of gelatin solution.*

(3) Based on present information, the optimal solution mentioned above shows slow but definite and continued degradation at temperatures encountered in certain theaters of war.

(4) The viscosity of the optimal solution is definitely greater than whole blood.

(5) It is not known whether a solution of this type will impair the return of normal function to kidneys in sustained ischemia or in the case of severe burns or the crush syndrome.

(6) Gelatin solutions probably do not contribute significantly to nutrition. Their only place in medical therapy appears to be to restore a loss of circulating blood volume in acute injury of various types.

(7) The influence of gelatin on the equilibrium in the distribution of plasma proteins between circulating blood and tissues should be further investigated.

*The solution with optimal value in the treatment of hemorrhage and shock examined up to the present time is one of 6 per cent concentration, prepared in saline, and with the general physicochemical characteristics of what is known as the "Knox P–20 type."

(*Notices on page xv*)